Identifying predictors to optimize treatment outcomes in patients with obstructive sleep apnea

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Het identificeren van voorspellers om de behandelresultaten te optimaliseren bij patiënten met obstructief slaapapneu
(met een samenvatting in het Nederlands)

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Chapter 1

General introduction and outline of this thesis

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Cassandra's prophecy

According to Aeschylus' tragedy Agamemnon, the Trojan princess Cassandra was loved by the god Apollo who sought to win her love by means of the gift of seeing the future. Cassandra accepted the proposal, received the gift, and then refused the god her favors. As the enraged Apollo could not revoke a divine power, he added to it the curse that nobody would believe her prophecies. She warned the Trojans about the Greeks hiding inside the wooden horse and accurately predicted the fall of Troy, but her warnings were ignored. In modern usage a Cassandra's prophecy is a metaphor to indicate an accurate prediction that doesn't find belief - usually to the harm of the disbelievers[1].

Figure 1.1 The Trojan princess Cassandra

Sleep disorders & Sleep-related breathing disorders

Humans spend nearly one third of their lives asleep. The impact of sleep quality on our health cannot be underestimated[2]. Sleep disorders are common and carry a significant healthcare burden. The most widely used classification for sleep disorders is the International Classification of Sleep Disorders (ICSD). The latest edition (ICSD-3) comprises seven major categories of sleep disorders: insomnia disorders, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, sleep-related movement disorders and other sleep disorders[3,4].

Sleep-related breathing disorders (SBD) are characterized by abnormal respiration during sleep. In general, sleep related breathing disorders can be divided into four categories: obstructive sleep apnea (OSA), central sleep apnea (CSA), sleep-related hypoventilation and sleep-related hypoxemia disorder. In patients with CSA, an apnea occurs because the brain doesn't send proper signals to the muscles that control breathing. In patients with OSA apneas are caused by upper airway obstruction and the brain function is not impaired. In the clinical setting, patients often meet the criteria for more than one sleep-related breathing disorder[3–5].

Obstructive sleep apnea

Definition

Obstructive sleep apnea is the most common sleep-related breathing disorder and is characterized by repetitive partial (hypopnea) or complete (apnea) upper airway obstruction which often results in decreased arterial oxygen saturation and arousal from sleep[6]. OSA is defined according to the criteria of the International Classification of Sleep Disorders (ICSD) and the scoring rules of the American Academy of Sleep Medicine (AASM). The criteria for OSA diagnosis according to the ICSD-3 are an apnea-hypopnea index (AHI) of ≥ 5 predominantly obstructive respiratory events per hour in combination with the presence of ≥1 OSA-associated symptoms; like sleepiness, arousals, observed snoring or apneas or the presence of associated comorbidities like hypertension[4–8] or an AHI of ≥15 predominantly obstructive respiratory events per hour even in the absence of OSA related symptoms or comorbidities *(Table 1.1).*

Table 1.1 Diagnostic criteria for OSA (adults)[4].

A	The presence of ≥1 of the following: • Complaints of sleepiness, non-restorative sleep, fatigue, or insomnia symptoms • Breath holding, gasping or choking symptoms which causes waking-up • Reported habitual snoring and/or breathing interruptions by bed partner • Diagnosis with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, CHF, artrial fibrillation, or type 2 diabetes mellitus
B	PSG or out of center sleep testing demonstrates ≥5 predominantly obstructive respiratory events per hour of sleep
C	PSG or out of centre sleep testing demonstrates ≥15 predominantly obstructive respiratory events per hour of sleep

The presence of the combined criteria A and B or the sole criterium C both meet the diagnosis of clinically obstructive sleep apnea syndrome.

Prevalence and risk factors

A systematic review written in 2017 described the overall prevalence of OSA to be 9 to 38%[9]. A more recent literature-based analysis suggests that 1 billion adults aged 30-69 years worldwide could have OSA defined as an AHI≥5, and the number of people with moderate to severe OSA (AHI≥15), for which treatment is generally recommended, is estimated to be almost 435 million[9,10]. The most common risk factors for OSA are male gender, increased age, obesity, and craniofacial and upper airway abnormalities. Less well-established risk factors include postmenopausal women, alcohol and smoking[11]. The prevalence appears to be increasing, this may be related to the increasing rates of obesity and increased detection rates of OSA[12]. Untreated OSA is an independent risk factor for hypertension and the development of cardiovascular diseases like coronary artery disease and stroke[13,14]. Additionally, patients with untreated OSA have a higher risk of being involved in a traffic accident as a consequence of excessive sleepiness[15,16].

Pathophysiology and symptoms

Obstructive sleep apnea involves a repetitive collapse of the upper airway during sleep, causing reduction (hypopnea) or cessation (apnea) of airflow resulting in hypoxemia associated with sleep fragmentation and possible cardiovascular and metabolic dysfunction[17]. Pathophysiologic causes of OSA include an anatomically compromised or collapsible upper airway defined by passive critical closing pressure of the upper airway (Pcrit); inadequate response of the upper airway dilator muscles to hypoxia and hypoxemia (decreased neuromuscular function); a higher degree of response to a ventilatory stimulus (loop gain) and a lower respiratory arousal threshold, causing waking up prematurely to airway narrowing[18–22]. Most patients with OSA complain of daytime sleepiness. Often bed partners report loud snoring, gasping or apneas[23]. Other common symptoms in patients with OSA include insomnia, nocturia and morning headaches[24–26]. When left untreated OSA gradually induces cognitive deficits and impairs performance[27].

Diagnosis

Clinical assessment

Consultation at the outpatient clinic should include a thorough history record including sleep history evaluating daytime and nighttime symptoms, sleep hygiene, sleep behavior (preferably by bedpartner), medication use (especially sedatives), medical history (especially cardiovascular diseases and diabetes mellitus type 2), consumption of alcohol

and tobacco and previous OSA treatment. The severity of daytime sleepiness can be evaluated using the Epworth Sleepiness Scale (ESS), a self-administered questionnaire that provides measurement of the patient's general level of daytime sleepiness. The ESS consists of 8 situations, allowing the patients to assess their degree of dozing off or falling asleep in a particular scene during the day, 0 for no dozing, and 1, 2, and 3 for slight, moderate, and high chance of dozing. A total score of ≥ 10 points is considered as excessive daytime sleepiness[28]. The Functional Outcomes of Sleep Questionnaire (FOSQ-30) and the subsequently introduced shorter version (FOSQ-10) are disease specific instruments designed to assess the impact of sleepiness on the ability to conduct daily activities[29,30]. Physical examination includes body mass index (BMI), neck circumference, assessment of the oropharynx including tongue size, tonsil size, webbing of the soft palate, length of the uvula and the Mallampati score, the presence of retro- or micrognathia and dental status.

Screening instruments

Several screening instruments have been developed to identify patients at risk for OSA. The AASM states that these screening tools should not be routinely used in asymptomatic patients in the community to screen for OSA[31]. However, these tools, in particular the STOP-Bang questionnaire are increasingly used as preoperative evaluation tools to evaluate those at risk for OSA and related perioperative complications. The STOP-Bang questionnaire consists of four questions (snoring, tiredness, observed apneas, and hypertension) plus four demographic queries (BMI>35 kg/m^2, age >50 years old, neck circumference >40 cm and male gender). For each question, answering 'yes' scores 1, a 'no' scores 0. With a total range of 0-8, a total score of ≥3 points is considered as a high probability for OSA[32]. The NoSAS score is a 5-item questionnaire which includes neck circumference, obesity, snoring, age, and gender. With a range of 0-17, NoSAS scores 4 points for neck circumference ≥40 cm, 3 points for BMI 25-30 kg/m^2, 5 points for BMI≥30 kg/m^2, 2 points for snoring, 4 points for age >55 years old, and 2 points for male gender. The total score of ≥8 points is considered as a high probability for OSA[33]. The ESS, which was originally designed to assess the extent of daytime sleepiness, has also been suggested as a screening tool for identifying patients at high risk for OSA[28]. However, multiple authors have found the ESS to be inferior to other screening tools for identifying patients at high risk for OSA[34–37]. Other screening instruments to identify patients at risk for OSA include the Berlin questionnaire and the STOP questionnaire[38–40].

Sleep study

The gold standard to diagnose OSA is a full-night polysomnography (PSG), including electroencephalography (EEG), electrooculography (EOG), surface electromyography (EMG), electrocardiography (ECG) or heart rate, nasal airflow and air temperature, thoracoabdominal movements, pulse oximetry, body position and snoring sounds. Scoring of the electronic raw data should be performed according to the AASM scoring manual, preferably by an experienced sleep investigator[41]. An apnea is defined as a decrease of at least 90% of airflow from baseline for ≥10 seconds. A hypopnea is defined as a decrease of at least 30% of airflow from baseline for ≥10 seconds, associated with either an arousal or ≥3% arterial oxygen saturation decrease. The mean number of apneas and hypopneas per hour of sleep is defined as the apnea-hypopnea index (AHI). The oxygen desaturation index is defined as the mean number of arterial oxygen desaturations ≥3% (ODI≥3%) or ≥4% (ODI≥4%) per hour[8]. Other diagnostic instruments to diagnose OSA are respiratory or ambulatory polygraphy (PG) - a simplified recording including airflow, respiratory effort, heart rate and oxygen saturation, without EEG, EOG, EMG and ECG -, home-based sleep studies and limited-channel devices (one or two channels, including oxygen saturation and/or airflow). Selecting the proper test should be based on availability and pretest probability of OSA.

Drug induced sleep endoscopy

Drug induced sleep endoscopy (DISE) is a dynamic diagnostic evaluation tool to assess the degree, level, and configuration of upper airway obstruction in patients with OSA[42]. DISE is indicated when upper airway surgery or upper airway stimulation is considered or in case of failure of continuous positive airway pressure (CPAP) or oral appliance treatment (OAT). Less well established is the indication for DISE when OAT is considered. DISE is carried out in a quiet operating room or endoscopy suite with dimmed lights and an anesthesiologist to manage sedation. In the last update of the European Position Paper on DISE the use of propofol with target-controlled infusion (TCI) is recommended, since this provides stable and reliable sedation in comparison to manual infusion or bolus technique[43]. The optimal depth of sedation is achieved when the patient begins to snore and/or no awakening from vocal or tactile stimuli is achieved. Once a proper level of sedation is approached, the upper airway is assessed in supine position by flexible fiberoptic laryngoscopy. There are several classification systems described in literature, but the most widely used is the VOTE classification[44]. This classification system is commonly used to assess levels and structures that may contribute to upper airway obstruction, namely velum (V), oropharynx (O), tongue base (T) and epiglottis (E). The degree of obstruction is defined as 0: no obstruction (collapse less than 50%), 1: partial collapse (between 50% and 75%, typically with vibration), or 2: complete collapse

(>75%). The configuration of obstruction is classified as anterior-posterior, lateral or concentric. Additionally, two maneuvers have been described in literature to mimic the effect of OAT. The chinlift maneuver; tilting the head backward and lifting the chin vertically upwards and the jawthrust maneuver; placing the practitioner's hands behind the angles of the mandible and thrust forward, bringing the lower incisors past the upper incisors, producing an anterior protrusion of the mandible.

Table 1.2 The VOTE classification.

Level	Direction		
	Anteroposterior	Lateral	Concentric
Velum			
Oropharynx			
Tongue base			
Epiglottis			

At each level, the degree and configuration of obstruction should be classified. Only one degree and configuration of obstruction can be scored on each level. Open boxes reflect the potential configuration that can be visualized. Shaded boxes reflect that a specific configuration cannot be objectified at this level.

Treatment

Lifestyle

Standard recommendations in patients with OSA include lifestyle alterations, such as weight reduction in overweight patients (BMI>25 kg/m^2), cessation of smoking, avoidance of sedatives and alcohol near bedtime and maintenance of a regular sleep rhythm[45,46]. However, weight reduction is often difficult in patients with untreated OSA because of the changed ratio in leptin a peptide that suppresses the appetite, and ghrelin that stimulates appetite[47,48].

Continuous positive airway pressure

CPAP is non-invasive and works as pneumatic splint preventing nocturnal collapse of the upper airway, reducing the AHI, and improving the quality of sleep[49,50]. In a Cochrane meta-analysis CPAP has shown to significantly reduce AHI as well as improve quality of life, cognitive function, and objective and subjective measures of sleepiness[51]. CPAP is the treatment of first choice in patients with moderate to severe OSA and is regarded as the gold standard treatment[52]. However, compliance and long-term use of CPAP is rather low[53]. Possible side effects contributing to CPAP intolerance are skin abrasion from contact with the mask, claustrophobia, mask leak, irritated eyes, excessive movements during sleep, nasal congestion, sneezing, gastric and bowel distension, and negative social factors. Additionally, in some cases CPAP leads to an insufficient decrease in residual AHI, referred to as CPAP failure upon efficacy. When symptoms remain

despite an adequate reduction in AHI, it is referred to as CPAP failure to diminish symptoms. In this case, other diagnoses should be considered.

Positional therapy

In a study evaluating the prevalence of positional obstructive sleep apnea (POSA) defined as a 50% reduction in the AHI between the supine and non-supine position, POSA was present in 27.4% of the patients. POSA was significantly more common in patients with a lower AHI, patients with a smaller neck circumference, and patients that spent more time in the supine position as a percentage of total sleep time[54]. In patients with POSA avoidance of the supine position is therefore a valuable therapeutic option. Positional therapy (PT) is aimed at preventing patients from sleeping in the supine position. The tennis ball technique uses a bulky mass strapped to the patient's back, ensuring that patients roll back on their side again. The new generation PT consist of a small device worn on the chest which vibrates if the patient sleeps on the back, stimulating the patients to roll back on their side[55].

Oral appliance treatment

In patients with mild to moderate OSA or in cases of CPAP intolerance, other treatment options include oral appliance treatment (OAT). The most frequently prescribed oral appliances for OSA are mandibular advancement devices (MAD), which are used intraorally at night to protrude the mandible and open the upper airway[56]. While OAT has lower efficacy than CPAP in terms of reducing the AHI, OAT has higher compliance rate and higher patient preference with fewer side effects, resulting in a similar overall therapeutic effectiveness in patients with mild and moderate OSA[57–59]. Finding predictors to select suitable patients that may benefit from OAT is therefore of great importance.

Upper airway surgery

Upper airway surgery aims to increase the volume of the upper airway, to remove specific pathology or to bypass the upper airway. Various surgical procedures are available for patients with OSA. Often, patients first undergo a DISE procedure to identify the site and pattern of obstruction and to identify whether they are a suitable candidate for upper airway surgery. Previously, uvulopalatopharyngoplasty (UPPP) was the most common procedure for palatal obstruction, creating more space retropalatal by resecting soft tissue[60]. In recent years, new surgical procedures have been described for patients with palatal obstruction including the expansion sphincter pharyngoplasty (ESP) and the barbed reposition pharyngoplasty (BRP)[61]. In patients with isolated oropharyngeal collapse due to tonsillar hypertrophy a classical tonsillectomy can be

considered without additional palatal surgery. In patients with tongue base obstruction various surgical procedures have been described in literature including radio frequent ablation of the tongue base (RFTB), midline glossectomy, genioglossus advancement, transoral robotic surgery (TORS), hyoid suspension and hypoglossal nerve stimulation[62-67]. In patients with collapse on the level on the epiglottis complete or partial epiglottidectomy can be considered[68]. Other more invasive forms of surgical therapy include maxillomandibular advancement (MMA) and tracheotomy[69,70].

Upper airway stimulation

Upper airway stimulation (UAS), also known as hypoglossal nerve stimulation, is the most recent development for treatment of moderate to severe OSA in patients with CPAP failure or intolerance. The most implanted UAS system produced by Inspire®, consists of a respiration sensor, programmable implanted pulse generator (IPG), and stimulating electrodes. The sensor is placed between the internal and external intercostal muscles and detects respiratory efforts from chest excursions that are analyzed by the IPG. The IPG is implanted below the clavicle and delivers stimulation synchronized with the respiratory cycle to the stimulation electrode. The stimulation electrode is placed on the anterior branches of the hypoglossal nerve and cervical spinal nerve 1 (C1). Stimulation of the anterior branches of the hypoglossal nerve causes a forward protrusion of the tongue by stimulating the genioglossus muscle. Furthermore, stimulation of C1 causes an anterosuperior displacement of the hyoid bone, both increasing the size of the oropharyngeal airway. Additionally, previous studies have shown that the effect of upper airway stimulation is not limited to the level of the tongue base, but also improves airway patency at the level of the palate caused by palatoglossal coupling[71].

Outline of this thesis

The ability to make accurate predictions remains up to our days an important asset. Unlike Cassandra, we now have a wide range of diagnostic tools at our disposition to make valid predictions. This is important to select optimal treatment modalities to assure beneficial treatment outcomes for OSA, that will not meet disbelief but can be trusted to benefit the patient. The general aim of this thesis is to identify predictors for patients at high risk for OSA and to find independent variables that can predict treatment outcome in patients with OSA.

In **Chapter 2,** the predictive performance of three different screening instruments for identifying patients at high risk for OSA is evaluated. In **Chapter 3,** DISE while administrating CPAP therapy is performed to identify potential causes for CPAP failure. Consequently, collapse patterns that could potentially predict the outcome of CPAP treatment are identified and suggestions are made for additional therapy. In **Chapter 4,** the predictive value of DISE with concomitant jaw thrust maneuver for treatment success of OAT is retrospectively evaluated. Based on the results of the study described in **Chapter 4,** in **Chapter 5** predictors during DISE for treatment success of OAT are prospectively validated. In **Chapter 6,** the long-term treatment outcomes of upper airway stimulation in patients with OSA are described. In **Chapter 7,** general conclusions and suggestions for future research are described. **Chapter 8** provides a summary of this thesis in Dutch.

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Chapter 2

Prediction of obstructive sleep apnea: comparative performance of three screening instruments on the apnea-hypopnea index and the oxygen desaturation index

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Abstract

Purpose

To evaluate the performance of the NoSAS (neck, obesity, snoring, age, sex) score, the STOP-Bang (snoring, tiredness, observed apneas, blood pressure, body mass index, age, neck circumference, gender) questionnaire, and the Epworth sleepiness score (ESS) as a screening tool for obstructive sleep apnea (OSA) severity based on the apnea-hypopnea index (AHI) and the oxygen desaturation index (ODI).

Methods

Data from 235 patients who were monitored by ambulant polysomnography (PSG) were retrospectively analyzed. OSA severity was classified based on the AHI; similar classification categories were made based on the ODI. Discrimination was assessed by the area under the curve (AUC), while predictive parameters were calculated by four-grid contingency tables.

Results

The NoSAS score and the STOP-Bang questionnaire were both equally adequate screening tools for the AHI and the ODI with AUC ranging from 0.695 to 0.767 and 0.684 to 0.767, respectively. Both questionnaires perform better when used as a continuous variable. The ESS did not show adequate discrimination for screening for OSA (AUC ranging from 0.450 to 0.525). Male gender, age, and BMI proved to be the strongest individual predictors in this cohort.

Conclusion

This is the first study to evaluate the predictive performance of three different screening instruments with respect to both the AHI and the ODI. This is important, due to increasing evidence that the ODI may have a higher reproducibility in the clinical setting. The NoSAS score and the STOP-Bang questionnaire proved to be equally adequate to predict OSA severity based on both the AHI and the ODI.

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repetitive partial or complete upper airway obstruction which often results in decreased arterial oxygen saturation and arousal from sleep[1]. OSA severity is commonly classified based on the apnea-hypopnea index (AHI)[2]. OSA has been associated with cardiovascular and metabolic consequences and is also linked with increased overall mortality[3]. Currently, overnight polysomnography (PSG) is the gold standard for diagnosing the presence and severity of OSA. However, its high expense, relative inaccessibility, and time consumption can delay or impede the diagnosis and treatment of patients with OSA, mainly in areas with limited healthcare resources[4]. Additionally, the increasing number of patients suspected of having OSA and the lack of structured patient interviews contribute to the growing number of patients being referred to sleep clinics[5]. Therefore, simple screening instruments for identifying patients at high risk for OSA have become increasingly important. Several instruments have been developed over the years including the STOP-Bang questionnaire[6,7] and the NoSAS score[8]. The STOP-Bang questionnaire shows a high sensitivity and negative predictive value, and therefore is a suitable instrument to rule out patients at risk for OSA[9–12]. However, it has a low to moderate specificity and it is possible that this will yield a high false-positive rate. Low specificity may result in unnecessary referral to sleep clinics for polysomnography[6,7]. The NoSAS score has been validated in multiple patient cohorts, and opinions concerning superiority over the STOP-Bang questionnaire differ[8,10,13–15]. The original validation of the NoSAS score by Marti-Soler et al. describes higher specificity and positive predictive values in comparison with the STOP-Bang questionnaire, while maintaining a moderate to high sensitivity and negative predictive value, therefore allowing to rule out clinically significant OSA and simultaneously reducing the number of unnecessary nocturnal recordings as well as the number of missed diagnosis[8]. The Epworth sleepiness scale (ESS), which was originally designed to assess the extent of daytime sleepiness, has also been suggested as a screening tool for identifying patients at high risk for OSA[16]. However, multiple authors have found the ESS to be inferior to other screening tools for identifying patients at high risk for OSA[11,12,17,18].

The present study reviewed and analyzed a cohort of 235 patients who underwent PSG, using in each case all three instruments: the STOP-Bang questionnaire[6], the NoSAS score[8], and the ESS[16]. Our main objectives were to evaluate the predictive and discriminative performance of the different screening instruments and compare the diagnostic effectiveness of the different methods. Additionally, we aimed to determine which variables independently were the strongest predictors in this cohort.

Recently, it has been suggested that the AHI is susceptible to variability in the clinical setting and that there is a need for an alternative parameter to indicate OSA severity[3,19-21]. An important disadvantage regarding the AHI is that the morphology and duration of the apneas are not taken into account. Longer, deeper apneas might be more significant than shorter, shallow ones[22]. Significant differences in the severity of OSA have been described between patients with a similar AHI[22]. Nocturnal oxygen desaturations are the result of apneas and are important in the pathogenesis and development of complications of OSA[23]. The arterial oxygen desaturation index (ODI) has therefore been proposed as an alternative for the AHI in grading PSG data and classifying OSA severity[23–26]. The ODI might be more relevant due to the higher reproducibility in the clinical setting[3,19–21]. Furthermore, there is evidence that the ODI is independently associated with prevalent risk factors like hypertension, whereas the AHI is not[19]. Therefore, in the present study, the discriminatory ability of the screening instruments will be evaluated by criteria based on the AHI as well as on the ODI.

Methods

Study design

Data from 235 patients who were monitored by ambulant PSG were retrospectively analyzed. Patient inclusion criteria were patients aging 18 years of age or older, completed clinical data, and completed STOP-Bang questionnaire and NoSAS score. Patient exclusion criteria were previously diagnosed OSA, use of portable sleep studies or respiratory polygraphy, incomplete clinical data, and technically inadequate PSG. In the outpatient clinic, the following clinical parameters were collected for all patients: gender, age, height, weight, body mass index (BMI), neck circumference (NC), self-reported complaints (snoring, daytime sleepiness, and apnea), and self-reported comorbidities (cardiovascular history, hypertension, pulmonary history). The ESS was completed. The clinical parameters were used to calculate the NoSAS score and the STOP-Bang questionnaire.

Screening instruments

The STOP-Bang questionnaire consists of four questions used in the STOP questionnaire—snoring, tiredness, observed apneas, and hypertension—plus four demographic queries—BMI>35 kg/m^2, age >50 years old, neck circumference >40 cm, and male gender. For each question, answering ‘yes’ scores 1, a ‘no’ scores 0. With a total range of 0–8, a total score of ≥3 points is considered as a high probability for

OSA[6]. The NoSAS score is a 5-item questionnaire which includes neck circumference, obesity, snoring, age, and gender. With a range of 0–17, NoSAS scores 4 points for neck circumference ≥40 cm, 3 points for BMI 25–30 kg/m^2, 5 points for BMI≥30 kg/ m^2, 2 points for snoring, 4 points for age >55 years old, and 2 points for male gender. The total score of ≥8 points is considered as a high probability for OSA[8]. The ESS consists of 8 situations, allowing the patients to assess their degree of dozing off or falling asleep in a particular scene during the day, 0 for no dozing, and 1, 2, and 3 for slight, moderate, and high chance of dozing. A total score of ≥10 points is considered as excessive daytime sleepiness[16].

Sleep study, scoring, and diagnosis

All patients underwent a full-night PSG at home. PSG included electroencephalography, electrooculography, surface electromyography, nasal airflow and air temperature, thoracoabdominal movements, pulse oximetry, body position, and snoring sounds. Breathing was recorded with nasal pressure and temperature sensors. Scoring of the electronic raw data was performed manually, following the recommendations of the American Academy of Sleep Medicine[2]. Apnea was defined as a decrease of at least 90% of airflow from baseline for >10 s. Hypopnea was defined as a decrease of at least 30% of airflow from baseline for >10 s, associated with either an arousal or ≥3% arterial oxygen saturation decrease. The mean number of apneas and hypopneas per hour of sleep (AHI) was calculated. The ODI was defined as the mean number of arterial oxygen desaturations ≥3% per hour. The severity of OSA was categorized both according to the AHI and to the ODI. By using the AHI, patients were classified as mild (5≤AHI<15 events/h), moderate (15≤AHI<30 events/h), or severe (AHI≥30 events/h) according to the 2012 American Academy of Sleep Medicine criteria[2]. For classification according to the ODI, patients were divided into similar groups: mild (5≤ODI<15 events/h), moderate (15≤ODI<30 events/h), and severe (ODI≥30 events/h)[27]. Other PSG parameters collected included the apnea index (AI), the AHI in supine position, the AHI in non-supine position, minimal arterial oxygen saturation (minimal SpO_2), baseline arterial oxygen saturation (baseline SpO_2), average arterial oxygen saturation (average SpO_2), and percentage of sleep time with arterial oxygen saturation time below 90% (SpO_2 time <90%).

Statistical analysis

The statistical analysis was performed by using Statistical Package for Social Studies (IBM SPSS Statistics version 24 for Windows, New York, NY, USA). Continuous data are presented as means with standard deviations. Categorical variables are presented as frequencies with percentages. Comparisons between groups were performed using Chi-

square tests for categorical variables, unpaired Student's t test, and univariate analysis of variance (ANOVA) for continuous variables. Discrimination, the ability of a screening tool to distinguish between patients with and without different outcomes, was estimated from the area under the curve (AUC) obtained by receiver operator characteristic (ROC) curves, which may range from 0.5 (no discrimination) to 1.0 (perfect discrimination)[28]. The AUCs were compared using the algorithm previously described by Hanley et al.[29]. Additionally, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for different AHI and ODI cut-offs using four-grid contingency tables, all estimates are reported with their respective 95% confidence interval (CI). The association between various individual demographic and clinical variables and the presence and degree of OSA was established by using a multivariate logistic regression model (backward stepwise selection, $p<0.05$). A two-tailed p value <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 201 patients met our inclusion criteria; baseline characteristics are mentioned in Table 2.1. A total of 148 (73.6%) patients were male, aged 50.0 ± 12.6 years, with a mean BMI of 28.0 ± 4.8 kg/m^2. Based on the AHI, OSA was present in 159 (79.1%) of the patients; 66 (41.5%) with mild OSA, 45 (28.3%) with moderate OSA, and 48 (30.2%) with severe OSA. Male gender, age, BMI, neck circumference, cardiovascular history, hypertension, snoring, and apneas were all significantly higher in the OSA groups than in the no OSA group. A post hoc Bonferroni test showed a statistically significant difference between no OSA and moderate/severe OSA for male gender (p=0.008; p=0.001), age (p=0.002; p=0.013), and BMI (p=0.045; p<0.001). BMI was also significantly different between mild/moderate OSA and severe OSA (p<0.001; p=0.030). Neck circumference (p=0.043; p=0.032), cardiovascular history (p=0.006; p=0.040), and hypertension (p=0.004; p=0.002) all showed a statistically significant difference between no/mild OSA and severe OSA. The ESS did not differ significantly between OSA groups (p=0.667; p=0.616). A total of 54.5%, 75.6%, and 85.4% of the patients in the mild, moderate, and severe OSA group, respectively, were classified as high risk of OSA according to the NoSAS score (cut-off ≥8; p<0.001). A total of 97%, 100%, and 100% in the mild, moderate, and severe OSA group, respectively, were classified as high risk of OSA according to the STOP-Bang questionnaire (cut-off ≥3; p<0.001). Polysomnography results (AHI, ODI≥3%, minimal SpO_2, average SpO_2, and SpO_2 time <90%) were all significantly different between the OSA and no OSA groups (p<0.001; p<0.001; p<0.001; p<0.001; p=0.001).

Notable is the percentage of patients with positional sleep apnea which was also statistically significant between the groups (p<0.001). A post hoc Bonferroni test shows that the difference was significant between no OSA and all OSA severity groups (p<0.001) and mild OSA and severe OSA (p=0.05).

Table 2.1 Baseline characteristics.

	All patients (n 201)	No OSA (AHI ≤5) (n 42)	Mild OSA (5≤AHI<15) (n 66)	Moderate OSA (15≤AHI<30) (n 45)	Severe OSA (AHI≥30) (n 48)	p value
Male patients	148 (73.6%)	22 (52.4%)	47 (71.2%)	37 (82.2%)	42 (87.5%)	*0.001*
Age (year)	50.0 ± 12.6	44.3 ± 11.0	49.3 ± 11.8	54.0 ± 11.0	52.3 ± 13.7	*0.002*
BMI (kg/m^2)	28.0 ± 4.8	25.9 ± 3.4	26.7 ± 4.2	28.5 ± 4.0	31.1 ± 5.8	*<0.001*
NC > 40 (cm)	100 (49.8%)	17 (40.5%)	28 (42.4%)	22 (48.9%)	33 (68.8%)	*0.020*
Cardiovasc. His.	59 (29.4%)	6 (14.3%)	15 (22.7%)	16 (35.6%)	22 (45.8%)	*0.004*
Hypertension	46 (22.9%)	5 (11.9%)	9 (13.6%)	12 (26.7%)	20 (41.7%)	*0.001*
Pulm. His.	7 (3.5%)	3 (7.1%)	1 (1.5%)	0 (0%)	3 (6.3%)	0.813[a]
Snoring	190 (94.5%)	38 (90.5%)	61 (92.4%)	43 (95.6%)	45 (100%)	*0.033*[a]
Sleepiness	166 (82.6%)	38 (90.5%)	50 (75.8%)	37 (82.2%)	41 (85.4%)	0.238
Apneas	148 (73.6%)	27 (64.3%)	43 (65.2%)	36 (80.0%)	42 (87.5%)	*0.018*
ESS[b]	5.8 ± 3.6	6.1 ± 3.9	5.4 ± 3.6	5.6 ± 3.4	6.1 ± 3.6	0.667
ESS ≥ 10[b]	35 (17.4%)	9 (21.4%)	12 (19.4%)	5 (11.4%)	9 (19.6%)	0.616
NoSAS	9.5 ± 4.0	7.3 ± 3.9	8.6 ± 3.5	10.3 ± 3.6	12.0 ± 3.5	*<0.001*
NoSAS ≥ 8	130 (64.7%)	19 (45.2%)	36 (54.5%)	34 (75.6%)	41 (85.4%)	*<0.001*
Stop-Bang	4.6 ± 1.4	3.8 ± 1.4	4.2 ± 1.2	4.8 ± 1.2)	5.5 ± 1.3	*<0.001*
Stop-Bang ≥3	192 (95.5%)	35 (83.3%)	64 (97%)	45 (100%)	48 (100%)	*<0.001*[a]
AHI (e/h)	20.5 ± 18.8	3.2 ± 1.2	9.5 ± 3.0	22.2 ± 4.1	49.1 ± 18.8	*<0.001*
ODI > 3% (e/h)	17.8 ± 17.3)	2.7 ± 1.4)	7.9 ± 3.3)	18.7 ± 5.2)	43.6 ± 14.5)	*<0.001*
Positional OSA	109 (54.2%)	0 (0%)	53 (80.3%)	30 (66.7%)	26 (54.2%)	*<0.001*
Min SpO_2 (%)	84.8 ± 7.3	89.5 ± 3.4	87.1 ± 5.2	84.9 ± 3.9	77.6 ± 9.4	*<0.001*
Average SpO_2 (%)	94.1 ± 2.0	95.1 ± 1.6	94.3 ± 1.9	93.9 ± 1.6	93.2 ± 2.2	*<0.001*
SpO_2 time <90% (%)	6.9 ± 14.8	3.0 ± 8.6	5.8 ± 17.2	4.5 ± 11.9	14.0 ± 15.9	*0.001*

Data are presented as mean ± standard deviation or number and percentage (%). Chi-square tests for categorical variables and ANOVA tests for continuous variables. *AHI* apnea-hypopnea index, *BMI* body mass index, *Cardiovasc. His.* cardiovascular history, *NC* neck circumference, *ODI* oxygen desaturation index, *Pulm. His.* pulmonary history. Italics is statistically significant; [a] Mann-Whitney *U* test; [b] Seven missing patients.

Performance of instruments

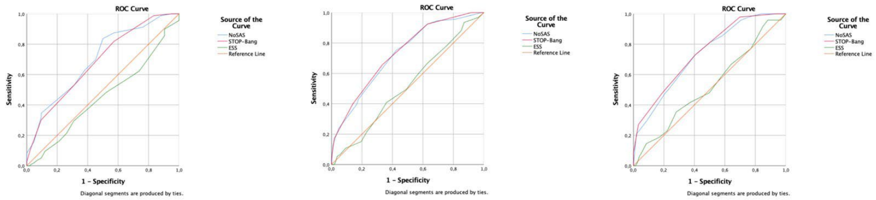
The predictive performance of the different screening instruments as categorical variable is shown in Table 2.2. For screening on different cut-off points of AHI and ODI severity, the sensitivity of the NoSAS score varies from 0.70 to 0.92 (AHI>5 and AHI>15, respectively). The specificity varies from 0.37 to 0.55 (AHI>15 and AHI>5, respectively). The STOP-Bang questionnaire showed the highest sensitivity varying from 0.99 to 1.00. However, the specificity was lower varying from 0.06 to 0.17. The highest specificity was obtained by the ESS, varying from 0.79 to 0.83, with a low sensitivity varying from 0.15 to 0.19. Figure 2.1 shows the ROC curves and the corresponding AUC of the three

screening instruments on different levels of AHI and ODI severity. The screening instruments are presented as continuous variables. The ESS did not show adequate discrimination for screening for AHI and ODI with an AUC ranging from 0.450 to 0.525. The NoSAS score and the STOP-Bang questionnaire were both equally adequate screening tools for the AHI and the ODI with AUC ranging from 0.695 to 0.767 and 0.684 to 0.767, respectively (all comparisons with *p* value >0.05). The discriminatory ability of the NoSAS score and the STOP-Bang questionnaire was similar in relation to both the AHI and the ODI (all comparisons with *p* value >0.05). When used as categorical variable, the AUC of the NoSAS score ranged from 0.620 to 0.684 (cut-off ≥8), the AUC of the STOP-Bang questionnaire ranged from 0.529 to 0.577 (cut-off ≥3) (Table 2.2). Both instruments performed better when used as continuous variable than as categorical variable. However, only for the STOP-Bang questionnaire, this difference proved to be significant (all comparisons except AHI ≥5 with *p* value <0.05).

Table 2.2 Performance of the NoSAS score, the STOP-Bang questionnaire, and the ESS.

		AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
AHI≥5 e/h	NoSAS	0.623 (0.525–0.720)	0.70 (0.62–0.76)	0.55 (0.40–0.69)	0.85 (0.78–0.90)	0.32 (0.23–0.44)
	STOP-Bang≥3	0.577 (0.473–0.681)	0.99 (0.96–1.00)	0.17 (0.08–0.31)	0.82 (0.76–0.87)	0.78 (0.45–0.94)
	ESS≥10	0.478 (0.378–0.579)	0.16 (0.11–0.23)	0.79 (0.64–0.88)	0.74 (0.58–0.86)	0.2 (0.15–0.27)
AHI≥15 e/h	NoSAS≥8	0.649 (0.573–0.725)	0.92 (0.85–0.96)	0.37 (0.29–0.46)	0.56 (0.48–0.63)	0.85 (0.72–0.93)
	STOP-Bang≥3	0.542 (0.462–0.621)	1.00 (0.96–1.00)	0.08 (0.04–0.15)	0.48 (0.41–0.55)	1.00 (0.70–1.00)
	ESS≥ 0	0.477 (0.395–0.558)	0.15 (0.09–0.24)	0.81 (0.72–0.97)	0.4 (0.26–0.56)	0.52 (0.45–0.6)
AHI≥30 e/h	NoSAS≥8	0.636 (0.552–0.720)	0.85 (0.73–0.93)	0.42 (0.34–0.5)	0.32 (0.24–0.4)	0.9 (0.81–0.95)
	STOP-Bang≥3	0.529 (0.438–0.620)	1.00 (0.93–1.00)	0.06 (0.03–0.11)	0.25 (0.19–0.32)	1.00 (0.70–1.00)
	ESS≥10	0.510 (0.414–0.606)	0.19 (0.1–0.32)	0.83 (0.76–0.88)	0.26 (0.14–0.42)	0.77 (0.7–0.82)
ODI≥5 e/h	NoSAS≥8	0.620 (0.531–0.709)	0.71 (0.63–0.78)	0.53 (0.4–0.65)	0.80 (0.72–0.86)	0.41 (0.30–0.52)
	STOP-Bang≥3	0.557 (0.464–0.650)	0.99 (0.95–1.00)	0.13 (0.06–0.24)	0.75 (0.68–0.81)	0.78 (0.45–0.94)
	ESS≥10	0.484 (0.392–0.575)	0.16 (0.11–0.23)	0.80 (0.68–0.88)	0.69 (0.52–0.81)	0.27 (0.2–0.34)
ODI≥15 e/h	NoSAS≥8	0.684 (0.610–0.757)	0.87 (0.78–0.93)	0.50 (0.41–0.58)	0.52 (0.44–0.61)	0.86 (0.76–0.92)
	STOP-Bang≥3	0.537 (0.456–0.617)	1.00 (0.95–1.00)	0.07 (0.04–0.13)	0.41 (0.34–0.48)	1.00 (0.7–1.00)
	ESS≥10	0.483 (0.400–0.567)	0.15 (0.09–0.25)	0.81 (0.74–0.87)	0.34 (0.21–0.51)	0.60 (0.53–0.67)
ODI≥30 e/h	NoSAS≥8	0.639 (0.553–0.724)	0.86 (0.73–0.94)	0.41 (0.34–0.49)	0.29 (0.22–0.38)	0.92 (0.83–0.96)
	STOP-Bang≥3	0.529 (0.435–0.622)	1.00 (0.92–1.00)	0.06 (0.03–0.11)	0.23 (0.18–0.29)	1.00 (0.70–1.00)
	ESS≥10	0.506 (0.407–0.606)	0.18 (0.1–0.32)	0.83 (0.76–0.88)	0.23 (0.12–0.39)	0.78 (0.71–0.84)

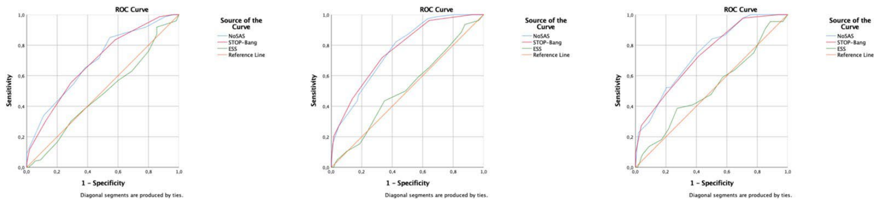
The screening instruments are presented as categorical variables (NoSAS≥8, STOP-Bang≥3, ESS≥10).
AHI apnea-hypopnea index, *AUC* area under the curve, *CI* confidence interval, *e/h* events/hour, *NPV* negative predictive value, *ODI* oxygen desaturation index, *PPV* positive predictive value.



AUC	NoSAS: 0.699 (0.610-0.788)	NoSAS: 0.723 (0.654-0.792)	NoSAS: 0.729 (0.652-0.807)
	STOP-Bang: 0.684 (0.593-0.775)	STOP-Bang 0.732 (0.664-0.800)	STOP-Bang 0.744 (0.668-0.821)
	ESS 0.450 (0.355-0.546)	ESS 0.517 (0.437-0.597)	ESS 0.525 (0.431-0.619)

2

	ODI ≥ 5	ODI ≥ 15	ODI ≥ 30



AUC	NoSAS: 0.695 (0.614-0.775)	NoSAS: 0.767 (0.703-0.830)	NoSAS: 0.745 (0.667-0.822)
	STOP-Bang: 0.689 (0.607-0.771)	STOP-Bang: 0.767 (0.703-0.832)	STOP-Bang: 0.737 (0.658-0.817)
	ESS: 0.482 (0.391-0.572)	ESS: 0.519 (0.438-0.601)	ESS: 0.521 (0.422-0.619)

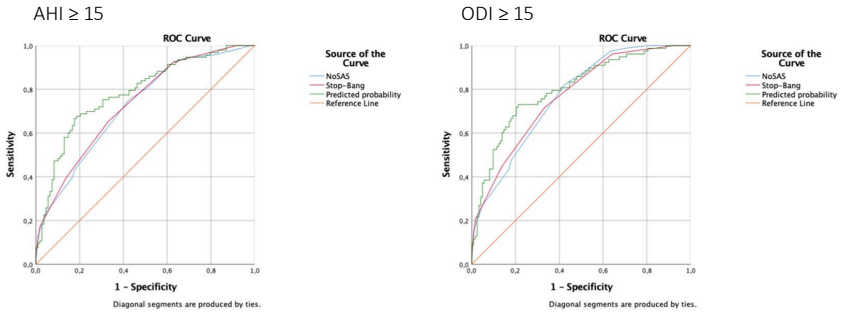
Figure 2.1 Discriminatory ability reported as area under the curve (AUC) (95% CI). The NoSAS score, the STOP-Bang questionnaire, and the ESS are presented as continuous variables. OSA severity is classified based on AHI≥5 (any OSA), AHI≥15 (moderate to severe OSA), and AHI≥30 (severe OSA). The ODI≥3% is subdivided into ODI≥5, ODI≥15, and ODI≥30. The NoSAS score performed similar when compared with the STOP-Bang questionnaire on all cut-off points (all comparisons with p value >0.05). The ESS presented lower discrimination than presented by the NoSAS score and the STOP-Bang questionnaire on all cut-off points (all comparisons with p value <0.05)

Predicting OSA

Multivariate logistic regression analyses were performed in order to establish the association between various individual demographic and clinical variables and the presence and degree of OSA categorized by the AHI and the ODI. Gender, age, and BMI proved to be the strongest predictors for any OSA (AHI≥5) (p<0.001; p<0.001; p=0.004), moderate to severe OSA (AHI≥15) (p<0.001; p<0.001; p<0.001), ODI≥5 (p=0.001; p=0.001; p=0.001), and ODI≥15 (p<0.001; p<0.001; p<0.001). Gender, BMI, and self-reported history of hypertension proved to be or the strongest predictors for severe OSA (AHI≥30) (p=0.028; p<0.001; p=0.028) and ODI≥30 (p=0.024; p<0.001; p=0.034).

The ROC curves of the estimated predictive probability, the NoSAS score, and the STOP-Bang questionnaire with cut-off points AHI≥15 and ODI≥15 are shown in Figure 2.2. The AUC of the estimated predicted probability was 0.784 when differentiating for AHI≥15 and

0.805 when differentiating for ODI≥15. The predicted probability performs similar to the NoSAS score and the STOP-Bang questionnaire (all comparisons with *p* value >0.05).



	AHI ≥ 15	ODI ≥ 15
AUC	Predicted probability 0.784 (0.721-0.848) NoSAS 0.723 (0.654-0.792) STOP-Bang 0.732 (0.664-0.800)	Predicted probability 0.805 (0.743-0.866) NoSAS 0.767 (0.703-0.830) STOP-Bang 0.767 (0.703-0.832)

Figure 2.2 Discriminatory ability reported as area under the curve (AUC) (95% CI). The NoSAS score and the STOP-Bang questionnaire are presented as continuous variables. The green ROC curve shows the plotted predicted probability of gender, age, and BMI. The predicted probability performs similar to the NoSAS score and the STOP-Bang questionnaire (all comparisons with *p* value >0.05). The ROC curves are presented at AHI≥15 and ODI≥15.

Discussion

The present study shows that both the NoSAS score and the STOP-Bang questionnaire, but not the ESS, were equally useful to detect patients at high risk for OSA. In this cohort, the STOP-Bang questionnaire had the highest sensitivity, with a low specificity. The NoSAS score had a higher specificity and PPV, while maintaining a moderate to high sensitivity. The ESS had the highest specificity, with a low sensitivity. This is in correspondence with what was found by previous authors[8,10,11,13,18,30]. The discriminatory ability of the NoSAS score and the STOP-Bang questionnaire was similar in relation to both the AHI and the ODI. However, due to the low specificity and positive predictive value of the STOP-Bang questionnaire, it is possible that the STOP-Bang will yield a large proportion of false-positive cases if used in a wrong patient group and therefore increase the number of unnecessary nocturnal recordings, whereas the NoSAS score describes higher specificity and positive predictive values, while maintaining a moderate to high sensitivity and negative predictive value.

The discriminatory ability of the NoSAS score and the STOP-Bang questionnaire as a categorical variable was compared with the discriminatory ability as a continuous

variable. As expected, the discriminatory ability is higher when the instrument is used as a continuous variable. However, only for the STOP-Bang questionnaire, this difference proved to be significant. Previous studies have already suggested that the probability of moderate to severe OSA increases in direct proportion to the STOP-Bang score, and therefore, the questionnaire should be used as a continuous rather than as a categorical variable. Chung et al. suggested patients with a STOP-Bang score of 0 to 2 to be classified as being at low risk for moderate to severe OSA. Those with a STOP-Bang score of 5 to 8 can be classified as being at high risk for moderate to severe OSA. In patients with a STOP-Bang score of 3 or 4, specific combinations of positive items should be examined further to ensure proper classification[6]. The NoSAS score has previously been presented as categorical variable with various cut-off points[8,10,13,14,30]. However, according to our study results, a similar scoring system to the STOP-Bang questionnaire can be considered. Coutinho Costa et al. suggested a similar approach, prioritizing patients depending on their score. Patients with a score of 0–5 are to be classified as low probability of OSA— particularly moderate to severe OSA; a score ≥7 are to be classified as probable OSA; a score ≥12 as a high probability of OSA—particularly moderate to severe OSA[14].

In the present cohort, male gender, age, and BMI showed to be the strongest individual predictors for OSA severity based on the AHI and the ODI. The discriminatory ability of the three variables combined was similar to the discriminatory ability of the NoSAS score and the STOP-Bang questionnaire. In future, this might present interesting opportunities to design a screening tool based on only three variables. As an alternative, the weighing factor of the variables gender, age, and BMI could be set higher in the existing screening instruments. A similar approach was suggested by Chung et al. for the STOP-Bang questionnaire, introducing male gender, BMI, and neck circumference as high-risk variables[6].

Clinical implications

This is the first study that evaluated the predictive performance of three different screening instruments with respect to both the AHI and the ODI. This is relevant, due to increasing evidence that the ODI has a higher reproducibility in the clinical setting[19–21]. Furthermore, significant differences in the severity of OSA have been described between patients with a similar AHI. Presumably, this is due to the fact that the morphology and duration of the apneas are not taken into account in the AHI[22]. In the present study, the NoSAS and STOP-Bang screening instruments both have a high discriminatory ability to predict OSA severity based on the AHI and the ODI. The ESS, however, was not able to

detect patients at high risk for OSA and should, therefore, not be used as a screening instrument.

Limitations and strengths

In general, the use of a retrospective analysis to validate the predictive value of different screening instruments is less ideal than a prospective study. In this observational study, however, our center had collected data prior to PSG monitoring, thus maintaining a high credibility for this retrospective study. Most patients were referred to the sleep clinic because they were suspected of having sleep-related problems. Therefore, it is possible that a selection bias was introduced, since the questionnaire was applied only to the suspected individuals. The great prevalence of OSA in this study population could affect the interpretation of the screening instruments. Contrarily, the present study has several important strengths: this is the first study that has evaluated the predictive value of different screening instruments on the ODI. As the ODI is gaining attention as new variable to classify OSA severity, this is an important new insight. Furthermore, all patients were evaluated with a full PSG and scored according to the current guidelines proposed by the American Academy of Sleep Medicine in 2012[2].

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Chapter 3

Drug-induced sleep endoscopy while administering CPAP therapy in patients with CPAP failure

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Abstract

Study objectives

To study the pattern of upper airway collapse in patients with CPAP failure by performing DISE while administering CPAP therapy and to determine the reason for CPAP failure accordingly.

Methods

This observational retrospective study comprised 30 patients diagnosed with OSA and CPAP failure, who underwent DISE while administering CPAP therapy. During DISE, the upper airway was assessed with and without CPAP therapy using the VOTE classification. Additionally, a jaw thrust maneuver was performed, in order to mimic the effect of an additional mandibular advancement device (MAD) in combination with CPAP therapy. Consequently, the outcome of DISE was translated into a clinically relevant categorization.

Results

Eleven patients (37%) had a persistent anteroposterior (AP) collapse, including a collapse at velum, tongue base, or epiglottis level and multilevel collapse. Eight patients (27%) had a floppy epiglottis. Five patients (17%) had a persistent complete concentric collapse (CCC) and three patients had a persistent laryngeal collapse (10%). In three patients (10%), no airway collapse was found after CPAP administration.

Conclusions

Based on the results of the reported study, in most cases, the potential cause of CPAP failure can be determined by this new diagnostic method. Consequently, suggestions can be made for additional therapy.

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repetitive partial or complete pharyngeal collapse causing reduction (hypopnea) or cessation (apnea) of airflow resulting in hypoxemia associated with sleep fragmentation, daytime sleepiness, and possible cardiovascular and metabolic dysfunction.[1,2]. OSA is a common condition globally. Population-based studies show that approximately 4% of men and 2% of women are affected by OSA[3]. In a more recent study, prevalence showed to be even higher with approximately 23% of women and 50% of men being affected[4]. Continuous positive airway pressure (CPAP) is unequivocally regarded as the gold standard treatment and often the treatment of first choice in patients with severe OSA. CPAP works as pneumatic splint preventing nocturnal collapse of the upper airway, reducing the apnea-hypopnea index (AHI), and improving the quality of sleep[5,6]. However, its effectiveness can be limited by adherence and tolerance, insufficient decrease in AHI, and limited improvement of symptoms[7]. In the present literature, the term CPAP failure is being used and interpreted in various ways including both poor tolerance and insufficient decrease in AHI. Recently, in order to create an unambiguous definition, a new nomenclature was proposed: (1) CPAP failure upon efficacy in case of an insufficient decrease in residual AHI above 5 apneas per hour, (2) CPAP failure to diminish symptoms when symptoms remain in spite of an adequate decrease in AHI, (3) CPAP intolerance in case of side effects and/or psychological reluctance, and (4) CPAP non-adherence in case of incorrect or insufficient use of CPAP[2]. Multiple studies have been performed to identify factors that influence or predict CPAP intolerance or non-adherence[7–10]. However, not much is known about predictors for CPAP failure upon efficacy (hereinafter referred to as “CPAP failure”).

Drug-induced sleep endoscopy (DISE), first described in 1991 by Croft and Pringle, is a diagnostic evaluation tool for the degree, level(s), and pattern of upper airway obstruction in patients with OSA[11,12]. DISE is often performed in order to consider other treatment options like surgical procedures, oral appliance treatment (including mandibular advancement devices), and upper airway stimulation. Recently, various studies have shown that DISE can be successful for CPAP titration; characteristics of airway collapse were evaluated as possible predictors for CPAP titration level[13-15]. However, to date, there are no studies that focus on evaluating the pattern of upper airway collapse while administering CPAP therapy to determine the cause of CPAP failure. In this paper, we give a detailed overview of our findings during DISE and identify the cause of CPAP failure individually. Consequently, suggestions will be made for additional therapy.

Material and methods

Study design and population

This study was designed as a retrospective, single-center descriptive cohort study including 30 consecutive patients diagnosed with CPAP failure due to an insufficient decrease in AHI above 5 apneas per hour. All patients were previously diagnosed with OSA which was either confirmed by polysomnography (PSG) or respiratory polygraphy (home sleep apnea test or PG) and were initially treated with CPAP. During follow-up, all patients experienced persistent OSA-related complaints and repeatedly measured an AHI above 5 apneas per hour despite intensive support and additional CPAP titration. Patients were extensively discussed in the multidisciplinary sleep team, composed of ENT-surgeons, neurologists, oral and maxillofacial surgeons, and pulmonologists and were diagnosed with CPAP failure. Drug-induced sleep endoscopy with and without administering CPAP therapy was carried out in order to identify the cause of CPAP failure. Subjects with and without previous nasal and/or pharyngeal surgery were included.

Drug-induced sleep endoscopy

Drug-induced sleep endoscopy was carried out in a quiet operating room with dimmed lights. All procedures were carried out by the same experienced ENT-surgeon (MC) with an anesthesiologist to manage sedation. Sleep was induced by an initial bolus of 1 mg/kg propofol followed by manual titration of propofol. The optimal depth of sedation was reached when the patient began to snore and/or no awakening from vocal or tactile stimuli was achieved. Once a proper level of sedation was approached, the upper airway was thoroughly observed by flexible fiberoptic laryngoscopy. The upper airway was assessed in supine position using the VOTE classification earlier described by Kezirian et al. (Table 3.1)[16,17]. This classification system is commonly used to assess levels and structures that may contribute to upper airway obstruction, namely velum (V), oropharynx (O), tongue base (T), and epiglottis (E). For each anatomical level, the configuration (anteroposterior, lateral, or concentric) and severity (no obstruction, partial obstruction, or complete obstruction) of the upper airway collapse were described. Subsequently, an adapted CPAP mask—allowing an endoscope to enter the nose, while permitting to increase CPAP pressures without air leakage—was adjusted (Figure 3.1). After the flexible laryngoscope was introduced into the nasal cavity via the adapted CPAP mask, CPAP therapy was started at a pressure of 6 cm H2O and gradually enhanced until the potential obstruction was discontinued or a pressure of 16 cm H2O was reached. Again, the upper airway was assessed by using the VOTE classification

while administering CPAP therapy. Additionally, a jaw thrust maneuver was performed, in order to mimic the effect of mandibular advancement device (MAD) in combination with CPAP therapy. The jaw thrust maneuver was called positive if the obstruction was discontinued on all levels. The jaw thrust maneuver was called negative if the obstruction was still present on one (or more) levels.

Table 3.1 The VOTE classification.

Level	Direction		
	Anteroposterior	Lateral	Concentric
Velum			
Oropharynx			
Tongue base			
Epiglottis			

At each level, the degree and configuration of obstruction should be classified. In each individual, only one degree and configuration of obstruction can be scored on each level. Open boxes reflect the potential configuration that can be visualized related to a specific structure. Shaded boxes reflect that a specific structure-configuration cannot be seen (for example, oropharynx lateral walls in an anteroposterior direction). The degree of obstruction is classified as: 0, no obstruction (no vibration, collapse <50%); 1, partial obstruction (vibration, collapse 50–75%); 2, complete obstruction (collapse >75%); x, not assessable.

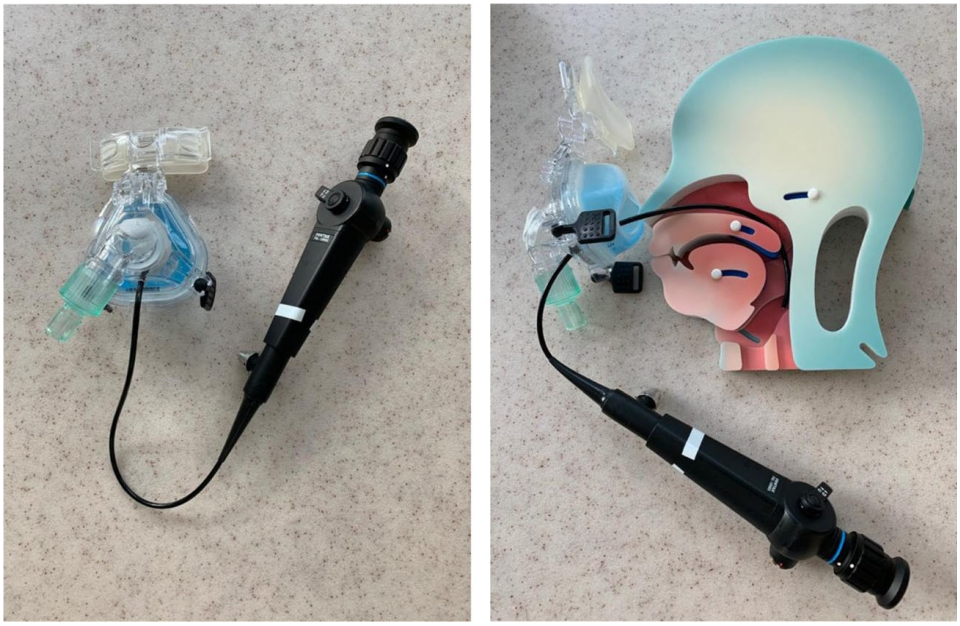

Figure 3.1 Front and side view of the adapted CPAP mask. The adapted CPAP mask has a small opening in front allowing an endoscope to enter the nose, while permitting to increase CPAP pressures without air leakage.

Statistical analysis

The statistical analysis was performed by using Statistical Package for Social Studies (IBM SPSS Statistics version 24 for Windows, New York, NY, USA). Descriptive statistics were accomplished to create the baseline characteristics. Continuous variables are presented as means with standard deviations. Categorical variables are presented as frequencies with percentages. Comparisons between groups were performed using chi-square test for categorical variables, Student's t test, and univariate analysis of variance (ANOVA) for continuous variables. For all analyses, a two-tailed p value of <0.05 was considered statistically significant.

Results

Baseline characteristics

The study population consisted of 30 patients. Patients were predominantly men (80%), with a mean age of 56.8 ± 13.0 years and a mean BMI of 28.6 ± 4.5 kg/m^2. Previous nasal/or pharyngeal surgery was performed in 13 patients (43%). In two patients (7%), uvulopalatopharyngoplasty was performed as previous OSA treatment. Nine patients (30%) underwent previous tonsillectomy. However, in all patients, the tonsillectomy was not OSA related. Two patients (7%) underwent previous closure of a cleft palate. The mean pre-treatment AHI was 42.1 ± 22.4 (7.0–96.0); the mean central breathing events per hour were 4.4 ± 6.9. The mean AHI with CPAP therapy was 26.0 ± 16.3 (5.7–69.4) (Table 3.2). The initial AHI and AHI with CPAP therapy are presented for each subject individually in Figure 3.2. A significant decrease in AHI after CPAP therapy with an average of 16.1 events per hour was found (95% CI, 10.0−22.3; p<0.0005). However, all patients experienced persistent OSA-related complaints and measured a residual AHI above 5 apneas per hour.

Table 3.2 Baseline characteristics of included patients with CPAP failure.

Patient characteristics	Mean ± SD	Range
Men[a]	24 (80%)	-
Age[b]	56.8 ± 13.0	30−78
BMI[c]	28.6 ± 4.5	17.9−38.6
Pretreatment AHI[d]	42.1 ± 22.4	7.0−96.0
AHI with CPAP therapy	26.0 ± 16.3	5.7−69.4

SD, standard deviation; *BMI*, body mass index; *AHI*, apnea-hypopnea index; *CPAP,* continuous positive airway pressure. [a] Gender is expressed as number and percentage (%) instead of mean ± SD; [b] Age in years; [c] BMI in kg/m^{2}; [d] AHI in apneas and hypopneas per hour.

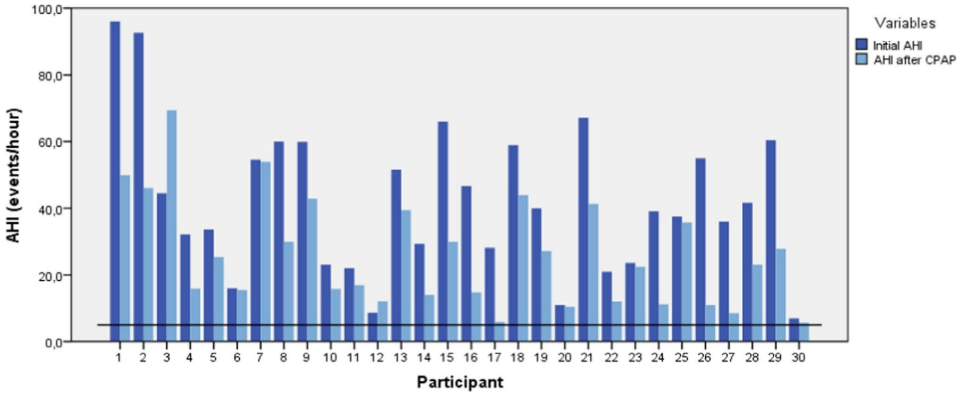

Figure 3.2 Bar graph showing the pretreatment AHI and AHI with CPAP therapy. Pretreatment AHI is presented in darker blue, AHI with CPAP therapy is presented in light blue. The horizontal black line indicates an AHI of 5 events/h.

DISE analysis

All patients underwent DISE, while CPAP was administered, during which no complications occurred. Table 3.3 shows DISE findings while administering CPAP therapy utilizing the VOTE classification. Figure 3.3 shows the distribution of the main outcomes. Eleven patients (37%) had a persistent anteroposterior (AP) collapse, including a collapse at velum, tongue base, or epiglottis level and a multilevel collapse. Eight patients (27%) had a floppy epiglottis. Five patients (17%) had a persistent complete concentric collapse (CCC) and three patients showed a laryngeal collapse (10%). In three patients (10%), no airway collapse was found after CPAP administration; in two patients, air leakage via the mouth was objectified, when closing the mouth CPAP therapy was effective. While administering CPAP therapy, a jaw thrust maneuver was performed. The obstruction was discontinued on all levels in 22 cases, two cases showed a persistent obstruction on one (or more) levels. In the three patients who did not have any upper airway collapse while administering CPAP, the jaw thrust maneuver was not performed. In the remaining three patients a jaw thrust maneuver was not reported.

Table 3.3 Overview of the distribution of the levels and pattern of upper airway collapse during DISE with CPAP.

Level	Direction								
	AP			Lateral			Concentric		
	None	Partial	Complete	None	Partial	Complete	None	Partial	Complete
Velum	46.7%	6.7%	30.0%	-	-	-	-	-	16.7%
Oropharynx				100%	-	-	-	-	-
Tongue base	76.7%	13.3%	10.0%						
Epiglottis	46.7%	10.0%	43.3%	-	-	-			

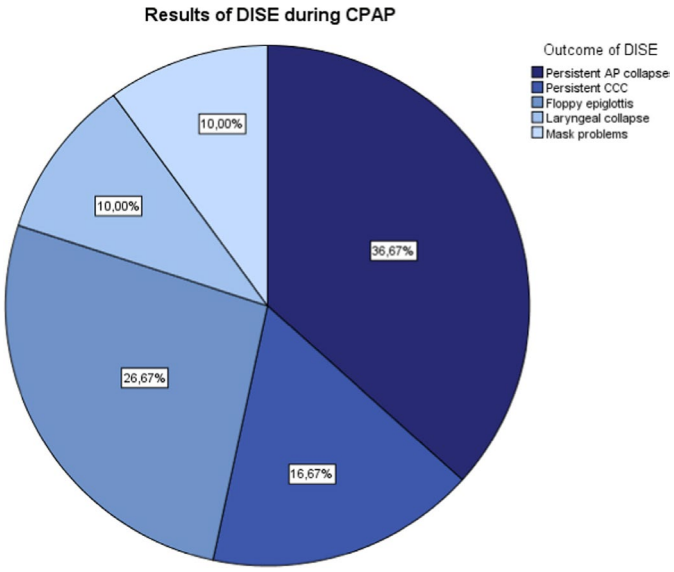

Figure 3.3 Distribution of outcome of the examination during DISE when CPAP therapy is administered.

The mean age, BMI, and AHI with CPAP therapy were compared between the different DISE outcomes. All variables were statistically significantly different for the different outcomes of DISE (p=0.060, p=0.019, and p=0.017respectively). An LSD post hoc test was done to specify between which groups the underlying difference was statistically significant. Firstly, patients with a persistent CCC were significantly younger than patients with a floppy epiglottis (p=0.043) or a laryngeal collapse (p=0.027). Patients with a laryngeal collapse were significantly older than patients encountering mask problems (p=0.031). Secondly, patients with a persistent CCC had a significantly higher BMI than patients with a persistent AP collapse (p=0.011) or floppy epiglottis (p=0.002). Lastly, comparing the groups based on their mean AHI with CPAP therapy, we found that patients with a persistent AP collapse had a significantly lower AHI than patients with a persistent CCC (p=0.015) or laryngeal collapse (p=0.026). Patients with mask problems had a significantly lower AHI compared to patients with persistent CCC (p=0.007) or laryngeal collapse (p=0.010).

Treatment

The distribution of different treatment options advised on account of the DISE outcome is shown in Figure 3.4. In 21 of the 22 patients with a positive effect of the jaw thrust maneuver, either a MAD or a MAD combined with CPAP therapy was advised. In the

other patient, a therapy including a MAD was impossible due to an edentate mandible. In four patients, a different CPAP mask was advised. One patient was advised to lose weight. In four patients, other treatment options were advised, including soft palate surgery, referral to a plastic surgeon because of CPAP failure due to an earlier unsuccessful operation of a cleft palate, and tracheotomy because of CPAP failure due to a laryngeal collapse at the level of the arytenoid cartilages.

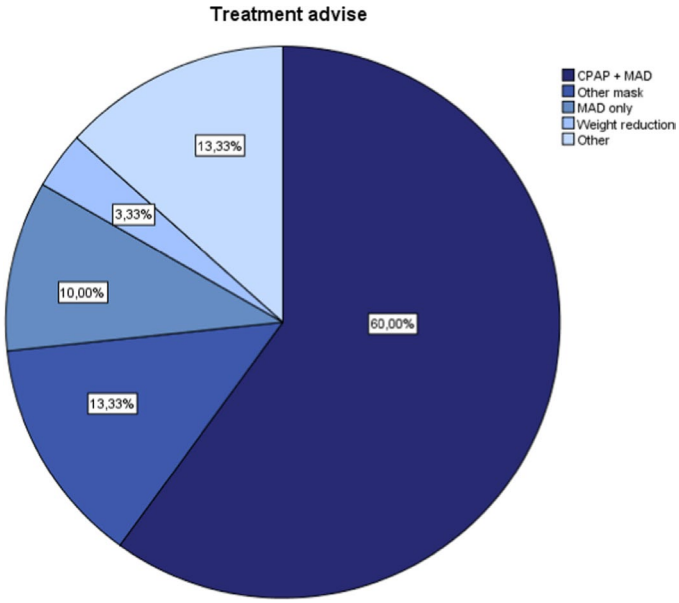

Figure 3.4 Distribution of the different treatment options advised on account of the DISE outcome.

Discussion

In this study, we were able to observe the effect of CPAP therapy on the pattern of upper airway collapse. Our findings show that a possible reason for CPAP failure can predominantly be identified. Previously, studies have been conducted to expand the utilization of DISE for CPAP titration and to evaluate possible predictors for CPAP titration level[14,15]. Additionally, studies have been conducted to evaluate the upper airway collapse in patients with CPAP failure[18,19]. However, to date there are no studies that focus on evaluating the pattern of upper airway obstruction while administering CPAP therapy. Acknowledging this problem, we believe that our results are highly relevant to the field. To the best of our knowledge, this is the first study to investigate the role of DISE while administering CPAP therapy as a method to

clarify possible mechanisms leading to CPAP failure and to address further treatment options. Our results may extent the utilization of DISE as a new diagnostic method in patients with OSA and CPAP failure.

In 2017, Torre et al. have shown that CPAP has a greater impact on the lateral walls of the oropharynx than it has on the velum, tongue base, or epiglottis[15]. A result that is endorsed by a study of Schwab et al.[20]. Our findings underline these observations since persistent lateral collapse of the oropharynx was not observed in our study. Another interesting finding is that some patients who were shown to have a floppy epiglottis during CPAP treatment were satisfied with this treatment for many years. This raises the question if this phenomenon might be instigated by long-term CPAP usage. Furthermore, in the present study, persistent CCC was associated with a higher BMI. The same observations were previously made by Hasselbacher et al. and Steffen et al.[19,21]. Additionally, patients with persistent CCC or laryngeal collapse had a higher AHI with CPAP therapy than patients with AP collapse. Previous authors have shown similar results; patients suffering from CCC have a significantly higher initial AHI[18,19,21]. In a recent study that focuses on DISE as a selection tool for upper airway stimulation by Vanderveken et al., it is stated that the absence of CCC can predict success of upper airway stimulation[22]. Our results indicate that, possibly, CCC is also a negative predictor for CPAP therapy. However, the sample size in our study was limited, so further investigations with larger sample sizes need to be conducted in the future to validate these results.

Limitations

This study has several limitations. It is obvious that assessment of the upper airway during DISE is based on subjective findings and therefore, prone to experience bias. However, previous studies have shown a moderate to substantial interrater reliability depending on the experience of the surgeon[23,24]. Furthermore, the degree of anesthetic depth and body position can alter the upper airway collapse[25,26]. Opponents of DISE argue that pharmacologically induced sleep, e.g., by propofol as in this study, is characterized by changing sleep patterns. Conversely, Rabelo et al. have shown that the AHI and other respiratory parameters remain unaffected[27]. It is nevertheless important not to oversedate[25]. Patients respond differently to propofol; therefore, it is stressed that the technique to elicit sleep must be standardized rather than to establish a universal concentration for all patients[27]. In this context, we used a consistent method of sedation in all patients by administering an initial bolus of 1 mg/kg. However, after the initial bolus, titration of propofol was administered manually until the patient began to snore and/or no awakening from vocal or tactile stimuli was achieved. In order to aim for a standardized technique, in future measuring sedation depth and the use of target-

controlled infusion pumps should be considered. It may also be discussed that the jaw thrust maneuver to mimic the effect of a MAD is a very imprecise maneuver as it lacks reproducibility and standardization. However, despite its limitations, performing a jaw thrust maneuver can easily and routinely be implemented during DISE and might improve patient selection for (additional) MAD treatment[28]. Undoubtedly, the retrospective nature and the small sample size of this study are the limitating factors. Testing for possible associations between the outcome of DISE and the befitting treatment was not applicable due to this small sample size. Additionally, the correlations found between DISE results and age, BMI, and AHI with CPAP therapy are based on a small sample size and therefore only tentative conclusions can be drawn. Studies with a larger sample size need to be conducted in the future in order to validate these results.

Conclusion

The results of this study provide important insight into the possible patterns of upper airway obstruction while administering CPAP therapy. In most cases, a possible cause of CPAP failure can be identified individually. Furthermore, we demonstrate that determining the reason of CPAP failure can lead towards new suggestions for treatment options in addition to/ instead of CPAP therapy, including surgery or an MAD. However, further analysis of the association between outcome of DISE and treatment options and analysis of the treatment outcome needs to be conducted in future studies.

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Chapter 4

Drug-induced Sleep Endoscopy: Are there Predictors for Failure of Oral Appliance Treatment?

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Abstract

Introduction

In the literature, evidence is lacking on the predictive value of drug-induced sleep endoscopy (DISE) for oral appliance treatment (OAT).

Objectives

The aim of the present study is to evaluate whether DISE with concomitant mandibular advancement maneuver can predict failure of OAT.

Methods

An observational retrospective study including patients diagnosed with obstructive sleep apnea (OSA) who previously received OAT. Results of DISE were analyzed in a group with documented OAT failure (apnea-hypopnea index [AHI] >10 events/hour or <50% reduction) and a group with OAT benefit (AHI <10 events/hour or >50% reduction). The upper airway was assessed using the velum, oropharynx, tongue base, epiglottis (VOTE) classification. Additionally, a mandibular advancement maneuver, manually protruding the mandible by performing a jaw thrust, was performed to mimic the effect of OAT.

Results

The present study included 50 patients with OAT failure and 20 patients with OAT benefit. A subgroup analysis of patients with OAT failure and an AHI <30 events/hour included 26 patients. In the OAT failure group, 74% had a negative jaw thrust maneuver. In the subgroup with an AHI <30 events/hour, 76.9% had a negative jaw thrust maneuver. In the OAT benefit group, 25% had a negative jaw thrust maneuver (p<0.001).

Conclusions

A negative jaw thrust maneuver during DISE can be a valuable predictor for OAT failure, independent of AHI. Drug-induced sleep endoscopy should be considered as a diagnostic evaluation tool before starting OAT.

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repetitive partial or complete upper airway obstruction that often results in decreased arterial oxygen saturation and arousal from sleep[1–4]. The current gold standard treatment of moderate to severe OSA is continuous positive airway pressure (CPAP).[5,6] However, compliance and long-term use of CPAP is rather low[7]. In patients with mild to moderate OSA or in cases of CPAP intolerance, other treatment options include oral appliance treatment (OAT), a non-invasive alternative to CPAP[2,3,6]. Mandibular advancement devices (MADs), which are used intraorally at night to advance the mandible, are the most common class of oral appliances[6]. Oral appliance treatment appears to have higher compliance rate and a higher patient preference, with fewer side effects and greater satisfaction when compared with CPAP therapy[8]. However, OAT is not always as effective in treating OSA. In a recent review article, approximately one-third of patients did not experience a therapeutic benefit[9]. Finding predictors to select suitable patients that may benefit from OAT is therefore of great importance. Various anthropometric and polysomnographic predictors for OAT have been described in the literature, including lower apnea-hypopnea index (AHI), lower body-mass index (BMI), lower age, female gender, and supine dependent OSA[10]. However, no diagnostic prediction tool for the effectiveness of OAT has been identified so far.

Drug-induced sleep endoscopy (DISE), first described in 1991 by Croft et al., is a diagnostic evaluation tool for the degree, level(s), and pattern of upper airway obstruction in OSA patients[2,11]. During DISE, a mandibular advancement maneuver is performed as a prediction tool for the effectiveness of OAT. However, opinions concerning the performance of a mandibular advancement maneuver during DISE vary among studies, and evidence on the positive and negative predictive values are limited so far[3,6,12–18]. Presently, patients are often prescribed OAT without evaluation of the upper airway through DISE. In case of ineffectiveness of OAT, there is a large delay in the appropriate treatment of the disorder and a waste of healthcare supplies.

In the present retrospective study, the DISE results from patients with documented OAT benefit, and OAT failure will be analyzed, and individual predictors for OAT failure will be identified. To the best of our knowledge, this is the first study to compare DISE results both of patients with OAT failure and with OAT benefit.

Material and methods

Study design and patient population

Data from 201 patients who were referred to this tertiary referral sleep center in the Netherlands between January 2017 and June 2019 were retrospectively analyzed. Patients referred to this center have repeatedly failed different therapies, and often present with CPAP- and OAT-failure or intolerance. Drug-induced sleep endoscopy is performed in all patients in order to consider other treatment options, such as surgical procedures and upper airway stimulation. The inclusion criteria were patients ≥18 years old, previous treatment with OAT (specifically MAD) and DISE with concomitant mandibular advancement maneuver performed in this hospital. A recent apnea-hypopnea index (AHI) measured by polysomnography (PSG) or respiratory polygraphy (PG or home sleep apnea test) had to be available. The exclusion criteria were patients with no history of OAT treatment, or OAT treatment different from a MAD, missing apnea-hypopnea index (AHI), or technically inadequate P(S)G, and if DISE was not performed in this hospital, or if a mandibular advancement maneuver was not performed. In the outpatient clinic, routine ear, nose, and throat (ENT) examination was performed. The following clinical parameters were collected for all patients: gender, age, height, weight, BMI, tonsil size (0–4), and Mallampati score[1–4].

Pretreatment sleep study

All patients were diagnosed with OSA, which was either confirmed by PSG or respiratory PG. The variables collected were AHI, oxygen desaturation index ≥3%, and oxygen desaturation index ≥4%, if available. Apnea was defined as a decrease of at least 90% of airflow from baseline for >10 seconds. Hypopnea was defined as a decrease of at least 30% of airflow from baseline for >10 seconds, associated with either an arousal or with ≥3% arterial oxygen saturation decrease. The mean number of apneas and hypopneas per hour of sleep (AHI) was calculated. The ODI ≥3% was defined as the mean number of arterial oxygen desaturations ≥3%. The ODI ≥4% was defined as the mean number of arterial oxygen desaturations ≥4%. The variables from the most recent sleep study were used in the analysis. If surgery was performed (for example, upper airway stimulation, pharyngoplasty), the last sleep study before surgery was used.

Drug-induced sleep endoscopy

Drug-induced sleep endoscopy was performed in a quiet operating room with dimmed lights. All procedures were performed by the same experienced ENT-surgeon (Copper, MP) with an anesthesiologist to manage sedation. Sleep was induced by an initial bolus

of 1 mg/kg propofol, followed by a titration of propofol. The optimal depth of sedation was reached when the patient began to snore and/or hypo responsiveness to vocal and tactile stimuli was achieved (Ramsay sedation level 5). Once a proper level of sedation was achieved, the upper airway was thoroughly observed by flexible fiberoptic laryngoscopy. The upper airway was assessed in the supine position using the velum, oropharynx, tongue base, epiglottis (VOTE) classification system as de- scribed by Kezirian et al. in 2011[19]. Upper airway collapse was evaluated on four different levels and structures, namely the velum (V), the oropharynx (O), the tongue base (T), and the epiglottis (E). The degree of obstruction was defined as 0: no obstruction (collapse <50%); 1: partial collapse (between 50% and 75%, typically with vibration); or 2: complete collapse (>75%). The configuration of obstruction can be classified as anteroposterior (AP), lateral (La) or concentric (Co)[2,19]. After the first assessment of the upper airway using the VOTE classification system, a mandibular advancement maneuver, manually protruding the mandible by performing a jaw thrust, was performed to mimic the effect of OAT. The hands of the practitioner were placed behind the angles of the mandible and thrust forward. The jaw thrust maneuver was performed without extensive force, bringing the lower incisors past the upper incisors by a couple of millimeters, producing a mild anterior protrusion of the mandible of ~75% of the maximal protrural range. The jaw thrust maneuver was called positive if the obstruction was discontinued on all levels. The jaw thrust maneuver was called negative if the obstruction was still present on one or more levels.

Data analysis

Our primary analysis describes the patient group with documented OAT failure. Oral appliance treatment failure was defined as an insignificant decrease in AHI on a follow-up sleep study (AHI >10 events/hour or <50% reduction from the baseline AHI). Oral appliance treatment intolerance, like temporomandibular dysfunction, dental pain or hypersalivation, was not counted as OAT failure. The secondary analysis describes the patient group with documented OAT benefit. Oral appliance treatment benefit was defined as a significant decrease in AHI on a follow-up sleep study (AHI <10 events/hour or >50% reduction from baseline AHI). One subgroup analysis was performed in the patient group with OAT failure. This subgroup analysis describes the patient group with documented OAT failure and an AHI <30 events/hour. This cut-off point was used to obtain comparable baseline characteristics. Furthermore, the Dutch guideline regarding OSA treatment states that OAT is not the first treatment choice in patients with an AHI >30 events/h.

Statistical analysis

The statistical analysis was performed by using IBM SPSS Statistics for Windows version 24 (IBM Corp., Armonk, NY, USA). Continuous data are presented as means with standard deviations (SDs). Categorical variables are presented as frequencies with percentages. Comparisons between groups were performed using chi-squared tests for categorical variables and the unpaired Student t test for continuous variables. The predictive performance of the jaw thrust maneuver for OAT failure was estimated from the area under the curve (AUC) obtained by receiver operator characteristic (ROC) curves. Additionally, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using four-grid contingency tables. All estimates are reported with their respective 95% confidence interval (CI). The association between various individual demographic data and clinical variables obtained from the sleep study test and DISE and the presence of OAT failure was established by using a multivariate logistic regression model (backward stepwise selection, $p<0.05$). All variables that were associated with OAT failure ($p<0.20$) were entered into the regression model. Additionally, a multivariate logistic regression analysis adjusted for confounding factors was used to assess the relation between OAT failure and the jaw thrust maneuver. A two-tailed *p*-value <0.05 was considered statistically significant.

Results

Baseline characteristics

Seventy patients met our inclusion criteria. The patients were subdivided in an OAT failure and an OAT benefit group; 50 patients with OAT failure were included in the primary analysis and 20 patients with OAT benefit were included in the secondary analysis. The subgroup analysis of patients with OAT failure and an AHI<30 events/hour included 26 patients (Figure 4.1).

Primary analysis - OAT failure (n=50)

Baseline characteristics are shown in Table 4.1. Sleep study data was obtained by PSG in 68% (34/50) of the patients and by PG in 32% (16/50) of the patients. A total of 84% (42/50) of the patients with OAT failure were male. The mean age was 57.2 ± 10.8 years old, with a mean BMI of 28.0 ± 2.8 kg/m^2, and a mean AHI of 31.1 ± 17.1 events/hour. The mean ODI ≥3% was 30.6 ± 16.8 events/hour, and the mean ODI ≥4% was 20.0 ± 15.2 events/hour. Previous tonsillectomy was performed in 36% (18/50) of the patients. The distribution of the levels and the pattern of upper airway collapse during DISE is shown

in Table 4.2. A total of 74% (37/50) of the patients with OAT failure had a negative jaw thrust maneuver (Table 4.1, Figure 4.2a).

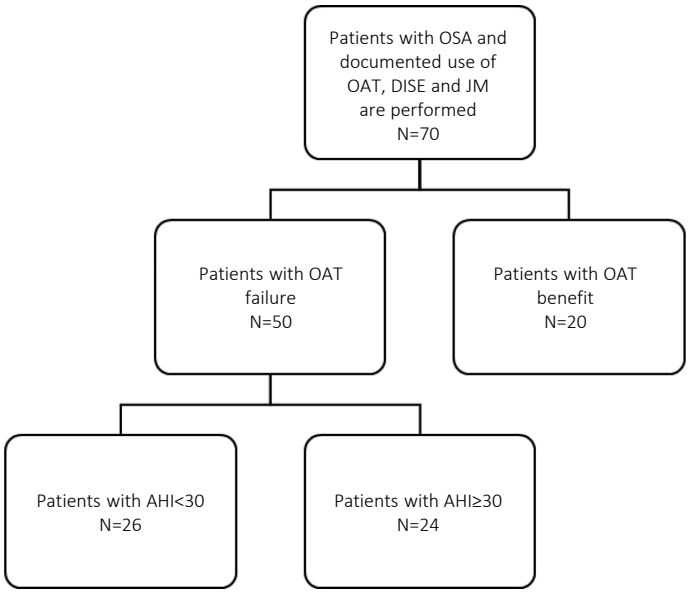

Figure 4.1 Flowchart of patient inclusion. AHI = apnea-hypopnea index. DISE = drug-induced sleep endoscopy. JM = jaw thrust maneuver. OAT oral appliance treatment. OSA = obstructive sleep apnea.

Secondary analysis - OAT benefit (n=20)

Baseline characteristics are shown in Table 4.1. Sleep study data was obtained by PSG in 90% (18/20) of the patients and by PG in 10% (2/20) of the patients. A total of 70% (14/20) of the patients with OAT benefit was male. The mean age was 55.6 ± 7.6 years old, with a mean BMI of 26.8 ± 2.9 kg/m^2, and a mean AHI of 22.8 ± 10.4 events/hour. The mean ODI ≥3% was 18.7 ± 10.2 events/hour, and the mean ODI ≥4% was 12.1 ± 8.8 events/hour. Previous tonsillectomy was performed in 70% (14/20) of the patients. The distribution of the levels and the pattern of upper airway collapse during DISE is shown in Table 4.2. A total of 25% (5/20) of the patients with OAT benefit had a negative jaw thrust maneuver (Table 4.1, Figure 4.2b).

Table 4.1 Baseline characteristics.

Baseline characteristics		Patients with OAT failure. (n=50)	Patients with OAT benefit. (n=20)	Significance (p-value)***	Patients with OAT failure and AHI<30. (n=26)	Significance (*p*-value)****
			Number (%)			
Male patients		42 (84)	14 (70)	0.202	22 (84.6)	0.292
			Mean ± SD			
Age in years		57.2 ± 10.8	55.6 ± 7.6	0.530	54.6 ± 11.1	0.739
BMI		28.0 ± 2.8	26.8 ± 2.9	0.103	27.6 ± 2.8	0.353
AHI		31.1 ± 17.1	22.8 ± 10.4	0.017	18.2 ± 6.4	0.069
ODI ≥3%		30.6 ± 16.8	18.7 ± 10.2	0.006	20.8 ± 9.0	0.487
ODI ≥ 4%		20.0 ± 15.2	12.1 ± 8.8	0.048	13.2 ± 7.8	0.704
			Number (%)			
Tonsil size	0	18 (36)	14 (70)	0.003	11 (42.3)	0.285*
	1	24 (48)	1 (5)		12 (46.2)	
	2	8 (16)	5 (25)		3 (11.5)	
	3	0 (0)	0 (0)		0 (0)	
	4	0 (0)	0 (0)		0 (0)	
Mallampati score**	1	4 (8)	1 (5.3)	0.827	3 (11.5)	0.392*
	2	15 (30)	6 (31.6)		9 (34.6)	
	3	11 (22)	4 (21.1)		6 (23.1)	
	4	20 (40)	8 (42.1)		8 (30.8)	
Degree of obstruction according to the VOTE classification (0–2):						
Velum		See Table 4.2		0.258*	See Table 4.2	0.520*
Oropharynx				0.131*		0.071*
Tonguebase				0.809		0.611*
Epiglottis				0.882*		0.444*
			Number (%)			
Negative jaw thrust maneuver		37 (74)	5 (25)	<0.001		<0.001

AHI, apnoea–hypopnoea index; BMI, body mass index; OAT, oral appliance treatment; ODI, oxygen desaturation index; SD, standard deviation.
* Mann-Whitney U test. ** 1 missing in OAT benefit group. *** *p*-value primary analysis (OAT failure vs OAT benefit). **** *p*-value subgroup analysis (OAT failure AHI<30 versus OAT benefit).

Sleep study data was obtained by PSG in 90% of the patients with OAT benefit and in 68% of the patients with OAT failure. This difference was statistically significant (p=0.01). The group with OAT benefit contained fewer male patients and had a lower average BMI than the group with OAT failure; however, these differences were not significant (p=0.202; p=0.103, respectively). The AHI, ODI ≥3% and ODI ≥4% were significantly lower in the group with OAT benefit (p=0.017; p=0.006; p=0.048, respectively). Additionally, the tonsil size was significantly lower in the group with OAT benefit (p=0.003). The percentage of negative jaw thrust maneuver in the OAT benefit group was significantly lower than in the OAT failure group (p<0.001).

Table 4.2 Overview of the distribution of the levels and pattern of upper airway collapse during DISE according to the VOTE classification.

Level	Direction								
	Anteroposterior			Lateral			Concentric		
	None	Partial	Complete	None	Partial	Complete	None	Partial	Complete
Patients with OAT failure (N=50)									
Velum	0 (0%)	3 (6%)	35 (70%)	–	–	–	–	–	12 (24%)
Oropharynx				36 (72%)	12 (24%)	2 (4%)			
Tongue base	8 (16%)	19 (38%)	23 (46%)						
Epiglottis	8 (16%)	16 (32%)	23 (46%)	–	2 (4%)	1 (2%)			
Patients with OAT benefit (N=20)									
Velum	0 (0%)	4 (20%)	12 (60%)	–	–	–	–	–	4 (20%)
Oropharynx				18 (90%)	1 (5%)	1 (5%)			
Tongue base	2 (10%)	8 (40%)	10 (50%)						
Epiglottis	2 (10%)	7 (35%)	11 (55%)	–	0 (0%)	0 (0%)			
Patients with OAT failure and AHI<30 (N=26)									
Velum	0 (0%)	2 (7.7%)	19 (73.1%)	–	–	–	–	–	5 (19.2%)
Oropharynx				17 (65.4%)	8 (30.8%)	1 (3.8%)			
Tongue base	5 (19.2%)	9 (34.6%)	12 (46.2%)						
Epiglottis	5 (19.2%)	9 (34.6%)	12 (46.2%)	–	0 (0%)	0 (0%)			

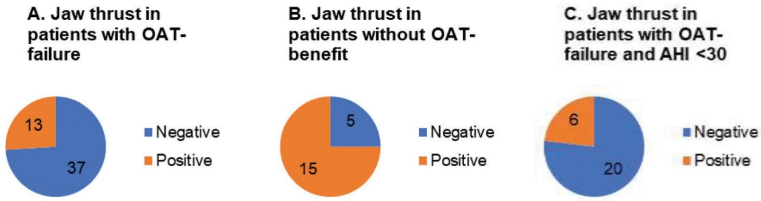

Figure 4.2 Outcome of the jaw thrust maneuver in all the patients with OAT failure (A), in patients with OAT benefit (B) and in patients with OAT failure and AHI<30 (C).

Subgroup analysis – OAT failure (AHI<30) (n=26)

Baseline characteristics are shown in Table 4.1. A total of 84.6% (22/26) of the patients with OAT failure and AHI<30 events/hour were male. The mean age was 54.6 ± 11.1 years old, with a mean BMI of 27.6 ± 2.8 kg/m^2, and a mean AHI of 18.2 ± 6.4 events/hour. The mean ODI ≥3% was 20.8 ± 9.0 events/hour, and the mean ODI ≥4% was 13.2 ± 7.8 events/hour. The distribution of the levels and the pattern of upper airway collapse during DISE is shown in Table 4.2. A total of 76.9% (20/26) of the patients with OAT failure and AHI<30 had a negative jaw thrust maneuver (Table 4.1, Figure 4.2c).

The group with OAT failure and an AHI<30 events/hour and the group with OAT benefit presented no significant differences in the baseline characteristics. The AHI in the OAT failure (AHI<30) group was lower than the AHI in the OAT benefit group; however, this difference was not significant (p=0.069). The percentage of negative jaw thrust maneuver in the OAT failure (AHI<30) group was significantly higher than in the OAT benefit group (p<0.001) (Table 4.1).

Prediction of treatment outcome

In the present patient cohort, the percentage of patients with a negative jaw thrust maneuver was significantly higher in the OAT failure group (p<0.001). The AHI, ODI ≥3%, ODI ≥4% and tonsil size were also significantly higher in the OAT failure group (p=0.017; p=0.006; p=0.048; p=0.003, respectively). Multivariate logistic regression analyses were performed to establish the association between individual demographic and clinical variables and the effectiveness of OAT. Adjusting for confounding factors like previous tonsillectomy, a negative jaw thrust maneuver and a higher ODI ≥3% proved to be the strongest predictors in the OAT failure group (p=0.003; p=0.029, respectively). Tonsil size did not prove to be a strong individual predictor in this group (p=0.364). In the subgroup analysis of patients with OAT failure and AHI<30 events/hour, only negative jaw thrust maneuver proved to be a strong predictor (p=0.001). The ROC curve in Figure 4.3a shows the discrimination of the jaw thrust maneuver between OAT failure and OAT benefit and has an AUC of 0.754 (95%CI: 0.614–0.876). The test sensitivity of the jaw thrust maneuver is 0.75 (95%CI: 0.53–0.89), and the test specificity is 0.74 (95%CI: 0.60–0.84). The PPV is 0.54 (95%CI: 0.36–0.70), and the NPV is 0.88 (95%CI: 0.75–0.95).

The ROC curve in Figure 4.3b shows the discrimination of the jaw thrust maneuver between OAT failure (AHI<30 events/hour) and OAT benefit and has an AUC of 0.760 (95%CI: 0.614–0.905) (Figure 4.3). The test sensitivity of the jaw thrust maneuver is 0.75 (95%CI: 0.53–0.89), and the test specificity is 0.77 (95%CI: 0.58–0.89). The PPV is 0.71 (95%CI: 0.5–0.86), and the NPV is 0.80 (95%CI: 0.61–0.91).

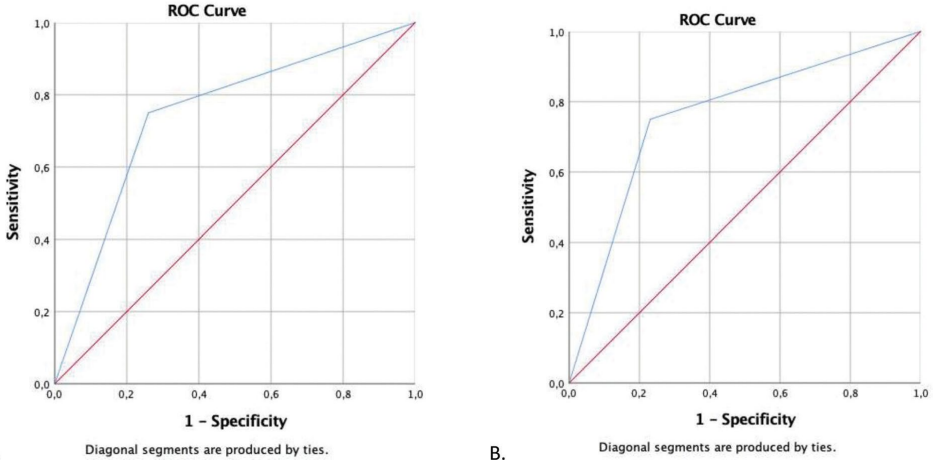

Figure 4.3 Receiver operating characteristic (ROC) curve. A. OAT failure versus OAT benefit. The AUC is 0.754 (95%CI: 0.614–0.876). B. OAT failure (AHI<30) versus OAT benefit. The AUC is 0.760 (95%CI: 0.614–0.905).

Discussion

The percentage of patients with a negative jaw thrust maneuver was significantly higher in the group with OAT failure in comparison with the group with OAT benefit. The AHI, ODI ≥3%, ODI ≥4% and tonsil size were also significantly higher in the patient group with OAT failure. In a recent study by Marklund et al., it was already described that a lower AHI is a predictor for benefit from OAT.[10] It could be argued that the results that we found are due to differences in AHI in the baseline characteristics of both patient groups, rather than to differences in outcome of the jaw thrust maneuver. To rule out this possible confounding bias in the analysis, a subgroup analysis was performed in patients with OAT failure and an AHI<30 events/hour. In this subgroup analysis, there were no significant differences in the baseline characteristics. The percentage of patients with a negative jaw thrust maneuver was found to be significantly higher in the patients with OAT failure (AHI<30 events/hour). Additionally, multivariate logistic regression analyses adjusted for confounding factors were performed to assess the relation between OAT failure and the jaw thrust maneuver. The jaw thrust maneuver proved to be the strongest predictor for OAT failure.

It must be acknowledged that 25% of the patients with OAT benefit had a negative jaw thrust maneuver. When only using the results of the jaw thrust maneuver to predict OAT failure, certain patients would not receive OAT although they would benefit from the therapy. The patients with OAT benefit and a negative jaw thrust maneuver had a lower BMI and a lower AHI in comparison with the patients with OAT benefit and a positive jaw thrust maneuver. However, these differences were not significant. These results are in line with those of previous studies, indicating that lower AHI and lower BMI are also important predictors for the success of OAT[10].

A total of 26% (13/50) of the patients with OAT failure had a positive jaw thrust maneuver. These patients were older and had a higher AHI in comparison with the patients with a negative jaw thrust maneuver. Again, these differences were not significant. Previously, Marklund et al. already described a higher AHI and older age to be predictors for OAT failure[10]. These results suggest that DISE with concomitant jaw thrust maneuver should be used together with anthropometric and polysomnographic predictors to accurately predict the success of OAT. Further prospective research needs to be done to develop a screening instrument for the effectiveness of OAT. Seventy percent of the patients in the OAT benefit group had undergone a previous tonsillectomy, in contrast with 36% in the OAT failure group (p=0.003; Table 4.1). In Table 4.2, it is shown that, in the OAT failure group, lateral collapse at the oropharyngeal

level (28%) was more common than in the OAT benefit group (10%). These results might indicate that previous tonsillectomy is a predictor for the success of OAT. This is in line with a previous study by Op de Beeck et al., who found that a complete lateral collapse at the oropharyngeal level is related to OAT failure[20]. However, a logistic regression analysis was performed, and tonsil size did not prove to be a strong individual predictor in this patient cohort. Adjusting for previous tonsillectomy, the jaw thrust maneuver proved to be a significant independent predictor.

Sleep study data was obtained by PSG from 68% of the patients with OAT failure and from 90% of the patients with OAT benefit. This difference was statistically significant (p=0.01). Previous studies have shown that the AHI is underestimated in PG[21,22]. If we take this into account, the mean AHI in the OAT failure group might be higher than the AHI that is presented, potentially influencing the outcome of patients with OAT failure. A logistic regression analysis was performed, and AHI did not prove to be a strong individual predictor in this patient cohort. Adjusting for the AHI, the jaw thrust maneuver proved to be a significant independent predictor.

Previously, other authors have tried to find a correlation between DISE results and OAT effectiveness. Battagel et al. and De Corso et al. have suggested that the effect of a mandibular protrusion <5 mm is predictive of OAT benefit[12,15]. Vanderveken et al. and Vroegop et al. have supported the concept of DISE with the addition of a simulation bite[3,6,23]. Vonk et al. demonstrated that a manual jaw thrust during DISE protruding the mandible at roughly between 50 and 75% of protrusion leads to an overestimation of the effect of OAT[2]. It is possible that this overestimation of the effect of OAT is present in the current study. Overestimation could account for the 13 patients in the OAT failure group with a positive jaw thrust maneuver. In a recent study by Huntley et al., the results of patients who underwent DISE and received OAT based on the recommendations during DISE were compared with a patient group who received OAT without prior selection by DISE. They found a significantly lower AHI and an increased number of patients reaching an AHI<5 with OAT in the DISE group[16]. These results are in line with the results of our study.

Clinical relevance

To the best of our knowledge, the present study the first study to compare the results of DISE in patients with OAT failure and OAT benefit. Additionally, the present study is the first study to analyze the predictive value of the jaw thrust maneuver for the effectiveness of OAT. Without suitable predictors for failure of OAT, there is an average to large percentage of patients that is inadequately treated for a short to longer period.

The findings of the present study are, therefore, of great importance for the prediction of the effectiveness of OAT. Furthermore, finding suitable predictors for selecting patients that will benefit from OAT will potentially have a beneficial effect on the cost reduction in OSA treatment. Additionally, it is expected that decreasing the group of inadequately treated OSA patients will have a favorable effect on cost reduction in OSA healthcare in general.

Limitations and strengths

The present study has several limitations. In the present study, the mandibular advancement maneuver was performed by manually performing a jaw thrust maneuver. Previous authors have criticized this technique, since it is nonreproducible and nontitratable and it does not account for vertical opening while closing the mouth, and state that the simulation bite is more accurate to predict the response to OAT[3,6,23]. However, in daily practice, the simulation bite technique might prove to be time-consuming and costly, potentially delaying and raising the cost of adequate OSA treatment, whereas performing a jaw thrust maneuver can easily and routinely be augmented to DISE. Additionally, it has been argued that the relaxation implied by the pharmacology necessary for DISE can possibly influence the tolerability for the jaw thrust maneuver, possibly leading to an overestimation of the OAT effect. Overestimation could possibly explain the patients in the OAT failure group with a positive jaw thrust maneuver. The assessment of the upper airway during DISE and the concomitant jaw thrust maneuver are based on subjective findings and, therefore, are prone to experience bias. Prior studies have shown DISE to be reliable and its interobserver reliability to be moderate to substantial, especially in experienced ENT surgeons[24–26]. In the present study, the jaw thrust maneuver was executed by one single surgeon and was identically performed in every individual according to the description in the method section. Thus, it can be expected that the jaw thrust maneuver was very similar in each individual. With the method description, it can easily be reproduced in daily practice in other healthcare institutions. However, the fact that the jaw thrust maneuver does not exactly simulate the effect of the OAT, the difficulty of reproduction and the lack of a better system to control the sedation does affect the internal and external validity of the study. Undoubtedly, the retrospective nature of the present study is a limiting factor. The present retrospective analysis was performed in a larger research design, and currently, prospective studies are being con- ducted to validate the observed retrospective correlations. The present study also has several important strengths; DISE was executed by one single surgeon and the jaw thrust maneuver was performed identically in every individual. Furthermore, this is the first study to analyze the predictive value of the jaw thrust maneuver for the effectiveness of OAT.

Conclusion

According to the present retrospective analysis, a negative jaw thrust maneuver can be a valuable independent predictor for OAT failure. Therefore, we suggest that DISE should be considered as a diagnostic evaluation tool to accurately predict the success of OAT. Based on the findings of the present retrospective study, we are currently prospectively evaluating the predictive value of the jaw thrust maneuver for the effectiveness of OAT.

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Chapter 5

The predictive value of mandibular advancement maneuvers during drug-induced sleep endoscopy for treatment success of oral appliance treatment in obstructive sleep apnea – a prospective study

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Abstract

Study objectives

To prospectively validate drug-induced sleep endoscopy (DISE) with mandibular advancement maneuvers as a prediction tool for treatment success of oral appliance treatment (OAT).

Methods

Seventy-seven patients diagnosed with moderate obstructive sleep apnea (OSA) were included and underwent DISE. The upper airway collapse was assessed using the VOTE classification. Additionally, three mandibular advancement maneuvers were performed to predict treatment success of OAT. If the maneuver was negative the level and degree and configuration of the persistent collapse was described according to the VOTE classification. All patients were treated with OAT and completed a follow-up sleep study with OAT in situ without regard to their anticipated response to treatment.

Results

Sixty-four patients completed 6-month follow up. A positive jaw thrust maneuver proved to be significantly associated with favorable OAT response, whereas the chin lift maneuver and the vertical chin lift maneuver were not. Additionally, a persistent lateral oropharyngeal collapse when performing any mandibular advancement maneuver was significantly associated with unfavorable OAT response.

Conclusion

The current findings suggest that a jaw thrust maneuver should be preferred over the chin lift maneuver for predicting OAT response. Patients with a positive jaw thrust maneuver should be counseled towards favorable OAT response, whereas those with persistent lateral oropharyngeal collapse should be advised about the likelihood of unfavorable OAT response. A negative jaw thrust maneuver did not prove to be a significant predictor for unfavorable response to OAT. Consequently, uncertainties arise regarding the justification of performing DISE solely for predicting the efficacy of OAT. However, the results of the current study could be influenced by heterogeneity in the assessment of respiratory parameters, variability in the performance of the mandibular advancement maneuvers and the instability of bolus technique sedation.

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repetitive partial or complete upper airway obstruction, which often results in decreased arterial oxygen saturation and arousal from sleep[1,2]. The gold standard treatment of moderate to severe OSA is continuous positive airway pressure (CPAP)[3,4]. In patients with mild to moderate OSA or in cases of CPAP intolerance, other treatment options include oral appliance treatment (OAT). The most frequently prescribed oral appliances for OSA are mandibular advancement devices (MAD), which are used intraorally at night to protrude the mandible and open the upper airway[5,6]. While OAT has lower efficacy than CPAP in terms of reducing the AHI, OAT has higher compliance rate and higher patient preference with fewer side effects, resulting in a similar overall therapeutic effectiveness in patients with mild to moderate OSA[7–10]. Response rate to OAT is patient dependent and depends on how treatment success is defined. Approximately one third of patients have a complete resolution of OSA defined as an AHI below 5/h, another one third of patients have a partial resolution of OSA defined as a 50% reduction in AHI, although AHI remains above 5/h and a third will not achieve >50% reduction in AHI[7,11–13]. Currently there is no validated clinical method to reliably pre-select patients that may benefit from OAT. Finding predictors to select patients who will receive sufficient treatment efficacy from OAT is therefore of great importance.

Previous studies have shown increased response for patients who are young and female, patients with a lower apnea-hypopnea index (AHI), a lower body-mass index (BMI) and supine-dependent OSA[14]. Additionally, different polysomnographic endotypes have been associated with OAT efficacy; lower loop gain, higher arousal threshold, lower ventilatory response and less severe airway collapsibility were all found to be independently associated with favorable OAT response[15–17]. Drug-induced sleep endoscopy (DISE) with mandibular advancement maneuvers to mimic the effect of OAT, has been proposed by several authors as a diagnostic prediction tool for OAT effectiveness[18–21]. However, opinions concerning the performance of a mandibular advancement maneuver vary among studies and evidence on the positive and negative predictive values are so far limited[20,22–26]. Additionally, there is growing attention to the different patterns of upper airway collapse during DISE and their possible prognostic value to OAT (i.e., DISE phenotypes). Three DISE phenotypes have been associated with OAT treatment outcome; one beneficial: tongue base collapse; and two adverse: compete concentric collapse at the level of the palate and complete laterolateral oropharyngeal collapse[27–29].

In this prospective study all patients underwent DISE with concomitant mandibular advancement maneuvers to predict success of OAT. All patients were treated with OAT and completed follow-up sleep study with OAT in situ, without regard to their anticipated response to treatment. The aim of this study was to prospectively validate DISE with concomitant mandibular advancement maneuver as a prediction tool for treatment success of OAT. According to prior retrospective research, the hypothesis was that patients with a negative mandibular advancement maneuver would not respond to OAT treatment[22].

Methods

Study design

A prospective single-center cohort study of consecutive patients diagnosed with moderate OSA with an AHI between 15 and 30 was performed. Patients were included if they met the inclusion criteria; patients of 18 years and older with OSA confirmed by respiratory polygraphy (PG), polysomnography (PSG) or 7 channel home sleep test (HST: WatchPat®), an AHI between 15-30 e/h and a BMI below 35 kg/m^2. Exclusion criteria were patients with ≥25% central apneas, edentulism, insufficient retention for OAT use, functional restrictions of the temporomandibular joint (TMJ), micrognathia and previous invasive upper airway surgery. In the outpatient clinic the following clinical parameters were collected for all patients: gender, age, height, weight, BMI, self-reported complaints (daytime sleepiness, arousals and snoring or apneas), tonsil size and Mallampati score. The Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ-30) were completed. Variables collected from the baseline sleep study were AHI, AHI in supine position, AHI in non-supine position, supine time in percentage, the oxygen desaturation index below 3% (ODI≥3%), the oxygen desaturation index below 4% (ODI≥4%), the obstructive apnea index, the central apnea index and the mixed apnea index, if available. Positional sleep apnea was defined as an AHI in non-supine position less than 50% of the AHI in supine position, a non-supine AHI of <10 e/h and a supine time between 10% and 90% of the total sleep time. All patients underwent DISE to evaluate the level and degree of collapse with three mandibular advancement maneuvers to predict the success of OAT and were referred to the department of Oral- and Maxillofacial Surgery for fitting of OAT. No difference was made between patients that were expected to benefit and patients that were expected not to benefit according to the response to the mandibular advancement maneuver. After six months of use, a respiratory polygraphy or HST was carried out with OAT in situ to evaluate treatment efficacy. Primary outcome measures were the AHI and the ODI≥3%. Secondary outcome

measures were the post-treatment ESS and FOSQ-30 questionnaire and complications (temporomandibular dysfunction (TMD), dental pain, gingival irritation, dry mouth, hypersalivation and dentofacial changes) (Figure 5.1).

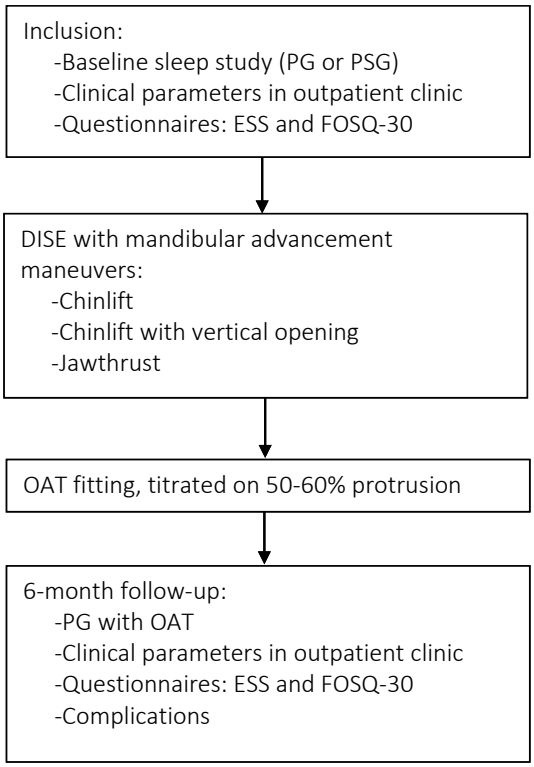

Figure 5.1 Study design.

Drug-induced sleep endoscopy

DISE was carried out in a quiet operating room with dimmed lights. All procedures were carried out by the same experienced ENT-surgeon and somnologist (MC) with an anesthesiologist to manage sedation. All procedures were captured on video and were available for later review. Sleep was induced by an initial bolus of 1 mg/kg propofol followed by manual titration of propofol. The optimal depth of sedation was reached when the patient began to snore and/or no awakening from vocal or tactile stimuli was achieved. Once a proper level of sedation was approached, the upper airway was thoroughly observed by flexible fiberoptic laryngoscopy. The upper airway was assessed in supine position using the VOTE classification earlier described by Kezirian et al.[30,31].

This classification system is commonly used to assess levels and structures that may contribute to upper airway obstruction, namely velum (V), oropharynx (O), tongue base (T) and epiglottis (E). The degree of obstruction is defined as 0: no obstruction (collapse less than 50%), 1: partial collapse (between 50% and 75%, typically with vibration), or 2: complete collapse (>75%). The configuration of obstruction is classified as anterior-posterior (AP), lateral (La) or concentric (Co). After this first assessment, three mandibular advancement maneuvers were performed to mimic the effect of OAT. First, a chin lift maneuver was performed, tilting the head backward and lifting the chin vertically upwards without excessive strength. Second, a chin lift maneuver was combined with a small vertical opening of the mouth with an interdental distance of about 1 cm. Third, a jaw thrust maneuver was performed, placing the practitioner's hands behind the angles of the mandible and thrust forward without extensive force, bringing the lower incisors past the upper incisors by a couple of millimeters, producing a mild anterior protrusion of the mandible of approximately 75% of the maximal protrural range. The maneuvers were called positive if the obstruction was discontinued on all levels. The maneuvers were called negative if the obstruction was still present on one (or more) levels. If the maneuver was negative, the level, degree and configuration of persistent collapse was described according to the VOTE classification.

Oral appliance therapy

Prior to inclusion, the dental status was assessed by an oral- and maxillofacial surgeon; clinical screening and orthopantomography (OPT) was performed. If a patient met the inclusion criteria, dental impressions were taken and a custom-made, two-piece titratable MAD (SomnoDent, SomnoMed, Australia) was fitted by a qualified dentist. The MAD consists of a maxillary and mandibular full coverage splint, the two splints are connected bilaterally with adjustable metal titration screws on the upper splint and triangular shaped wings on the lower splint. A bite fork was used to measure and register each patient's maximum mandibular protrusion capacity, and to determine the appropriate antero-posterior and vertical mandibular positions needed for the construction of the MAD. The MAD was placed at 50-60% of the individual patients' maximal protrusion. Acclimatization occurred over a period of approximately 2 months. During this time, the degree of mandibular advancement was titrated until the maximum comfortable limit was achieved and subjective complaints were reduced.

Definition of treatment response/deterioration

Treatment response was defined as a post-treatment AHI<15 e/h and a reduction of >50% in comparison to baseline AHI. Treatment deterioration was defined as an increase of >10% in comparison to baseline AHI.

Statistical analysis

The statistical analysis and graphical presentation were performed by using Statistical Package for Social Studies (IBM SPSS Statistics version 24 for Windows, New York, NY, USA) and Prism GraphPad (Version 9.3.1, San Diego, USA). Normality of the distribution was visually assessed by means of a histogram and a Q-Q plot. Normally distributed continuous data are presented as means with standard deviations. Categorical data are presented as frequencies with percentages. Comparisons between groups were performed using Student's independent *t* test for continuous variables and Chi-squared test for categorical variables. The predictive value of DISE outcomes on treatment response of OAT was established by using univariable and multivariable linear regression modelling. A two-tailed *p*-value <0.05 was considered statistically significant.

Sample size

We had no a priori formally statistically testable hypothesis. This study seeks to find such a hypothesis. Pragmatically, with regard to the sample size we could include 80 patients; on average 40 patients with a negative jaw thrust maneuver and 40 patients with a positive jaw thrust maneuver. With the smallest group of 40 patients and setting alpha = 0.05 and a treatment effect (before-after) of 0.5 (Cohen's d; treatment effect in terms of absolute effect divided by the standard deviation) we have 85% power to detect such a difference when using a paired *t* test.

Results

Study inclusion

Eighty-seven patients with OSA met the inclusion criteria; six patients did not sign the informed consent; three patients canceled the DISE, and one patient moved to another city. Seventy-seven patients underwent DISE; eight patients did not complete the study due to OAT intolerance; one patient never had an OAT fitting; three patients did not show up at follow-up respiratory polygraphy and one patient was excluded due to complicated hip surgery needing opioids causing central apneas and causing inability to

sleep on the side leading to only supine sleep position; 64 patients finished follow-up. No significant differences were found in the baseline characteristics of the patients lost to follow-up (n=13) and patients completing the follow-up (n=64) (Figure 5.2).

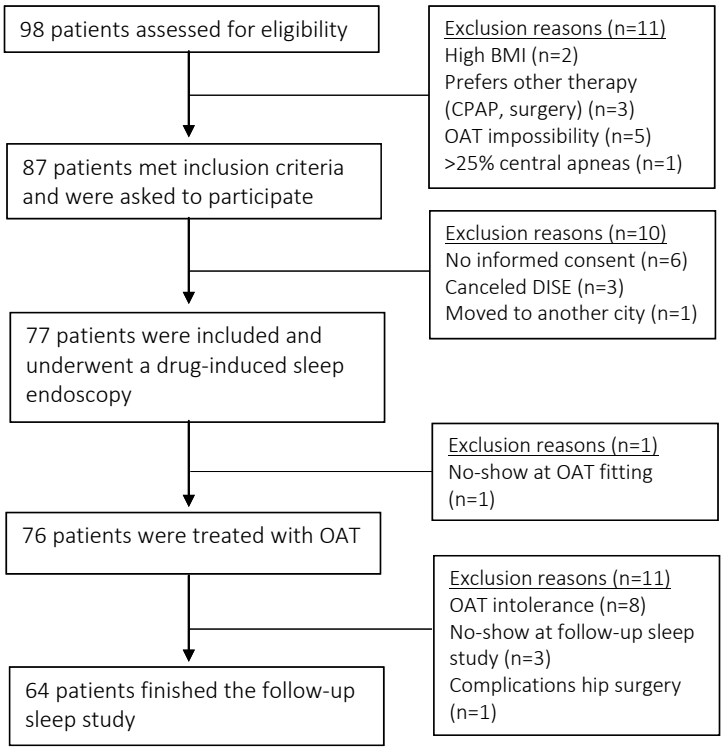

Figure 5.2 Flow-chart inclusions.

Baseline characteristics

In the entire cohort sixteen patients (25%) were female. The mean age was 49.7 ± 10.2 years, and the mean BMI was 28.6 ± 3.7 kg/m^2. Eighteen (28%) patients previously underwent a tonsillectomy. The mean pre-treatment AHI was 19.9 ± 4.2 e/h and the mean pre-treatment ODI≥3% was 19.9 ± 6.4 e/h. Nineteen patients (30%) had positional OSA. The mean ESS was 9.8 ± 5.3, the mean FOSQ-30 was 95.3 ± 17.4. Twenty-six patients (41%) had a positive jaw thrust maneuver, 12 patients (19%) had a positive chin lift maneuver, and 30 patients (47%) had a positive vertical chin lift maneuver. Response to treatment was seen in 36 patients (56%), deterioration was seen in 7 patients (11%). No significant differences were found in the baseline characteristics between responders

and non-responders and between deteriorating and non-deteriorating patients (Table 5.1).

Table 5.1 Baseline characteristics.

Baseline characteristics	Total sample (n=64)	Responder			Deterioration		
		Yes (n=36; 56%)	No (n=28; 44%)	*p**	Yes (n=7; 11%)	No (n=57; 89%)	*p**
Female patients (n (%))	16 (25%)	9 (25%)	7 (25%)	1.0	2 (29%)	14 (25%)	0.817
Age (mean ± SD; years)	49.7 ± 10.2	49.3 ± 9.3	50.3 ± 11.4	0.716	47.0 ± 11.5	50.1 ± 10.1	0.459
BMI (mean ± SD; kg/m^2)	28.6 ± 3.7	28.8 ± 3.6	28.4 ± 3.8	0.678	28.8 ± 3.1	28.6 ± 3.7	0.918
Previous tonsillectomy (n (%))	18 (28%)	10 (28%)	8 (29%)	0.944	1 (14%)	17 (30%)	0.388
AHI (mean ± SD; e/h)	19.9 ± 4.2	19.8 ± 4.2	20.0 ± 4.3	0.870	18.6 ± 4.0	20.0 ± 4.2	0.388
ODI ≥3% (mean ± SD; e/h)	19.9 ± 6.4	19.2 ± 6.1	20.8 ± 6.9	0.366	18.4 ± 4.1	20.1 ± 6.7	0.520
Positional OSA (n (%))	19 (30%)	11 (31%)	8 (29%)	0.863	3 (43%)	16 (28%)	0.419
ESS (mean ± SD; range: 0-24)	9.8 ± 5.3	10.1 ± 5.4	9.4 ± 5.2	0.592	8.7 ± 4.2	9.9 ± 5.4	0.568
FOSQ (mean ± SD; range: to 120)	95.3 ± 17.4	92.7 ± 19.0	98.6 ± 14.8	0.180	96.4 ± 16.0	95.1 ± 17.7	0.851
Jawthrust maneuver (positive; n (%))	26 (41%)	18 (50%)	8 (29%)	0.083	2 (29%)	24 (42%)	0.491
Chinlift maneuver (positive; n (%))	12 (19%)	8 (23%)	4 (14%)	0.389	1 (14%)	11 (20%)	0.734
Chinlift vertical maneuver (positive; n (%))	30 (47%)	19 (54%)	11 (42%)	0.355	3 (50%)	27 (49%)	0.966

AHI = apnoea–hypopnoea index; BMI= body-mass index; ESS= Epworth Sleepiness Scale; FOSQ-30= Functional Outcomes of Sleep Questionnaire; n= number; ODI = oxygen desaturation index; SD = standard deviation. *Chi-Square test for categorical variables; Student's independent *t* test for continuous variables

Post-treatment sleep study

The sleep study results are shown in Table 5.2*;* patients are categorized according to the mandibular advancement maneuvers. The post-treatment AHI in the entire cohort was 10.6 ± 7.6 e/h; the delta (Δ) AHI was -9.3 ± 8.0. The post-treatment ODI≥3% was 11.2 ± 7.9; the Δ ODI≥3 % was -8.7 ± 9.1. Patients with a positive mandibular advancement maneuver had a lower post-treatment AHI than patients with a negative mandibular advancement maneuver. However, only for the jaw thrust maneuver this difference proved to be significant (p=0.02). The post-treatment ODI≥3% was also significantly lower in the positive jaw thrust maneuver group (p=0.05) (Figure 5.3).

Table 5.2 Mandibular advancement maneuvers.

Variable	Total sample (n=64)	Chinlift (n=63)£			Chinlift vertical (n=61)¥			Jawthrust (n=64)		
		Positive (n=12; 19%)	Negative (n=51; 81%)	*p**	Positive (n=30; 49%)	Negative (n=31; 51%)	*p**	Positive (n=26; 41%)	Negative (n=38; 59%)	*p**
Pre-treatment AHI (e/h)	19.9 ± 4.2	18.1 ± 3.0	20.3 ± 4.4	0.105	20.1 ± 4.6	19.6 ± 3.9	0.634	19.4 ± 4.3	20.2 ± 4.2	0.470
Post-treatment AHI (e/h)	10.6 ± 7.6	8.4 ± 4.6	11.1 ± 8.2	0.262	8.8 ± 6.0	11.7 ± 8.3	0.131	8.0 ± 5.3	12.4 ± 8.5	**0.023**
Δ AHI (e/h)	-9.3 ± 8.0	-9.7 ± 5.3	-9.1 ± 8.7	0.827	-11.3 ± 7.8	-7.9 ± 7.9	0.099	-11.4 ± 6.7	-7.8 ± 8.6	0.078
Pre-treatment ODI ≥3% (e/h)	19.9 ± 6.4	16.9 ± 6.0	20.5 ± 6.4	0.081	20.4 ± 7.7	19.1 ± 4.9	0.455	19.7 ± 8.2	20.0 ± 4.9	0.865
Post-treatment ODI ≥3% (e/h)	11.2 ± 7.9	9.6 ± 5.3	11.6 ± 8.5	0.433	10.0 ± 6.9	11.8 ± 8.2	0.367	8.9 ± 5.9	12.9 ± 8.8	**0.047**
Δ ODI ≥3% (e/h)	-8.7 ± 9.1	-7.3 ± 6.2	-8.9 ± 9.7	0.592	-10.4 ± 9.3	-7.3 ± 8.7	0.196	-10.9 ± 8.7	-7.1 ± 9.2	0.114

AHI = apnoea–hypopnoea index; n = number; ODI = oxygen desaturation index. Numbers are presented as means with SD (standard deviation). £1 missing patient; ¥3 missing patients. * Student's independent t test. Bold is statistically significant.

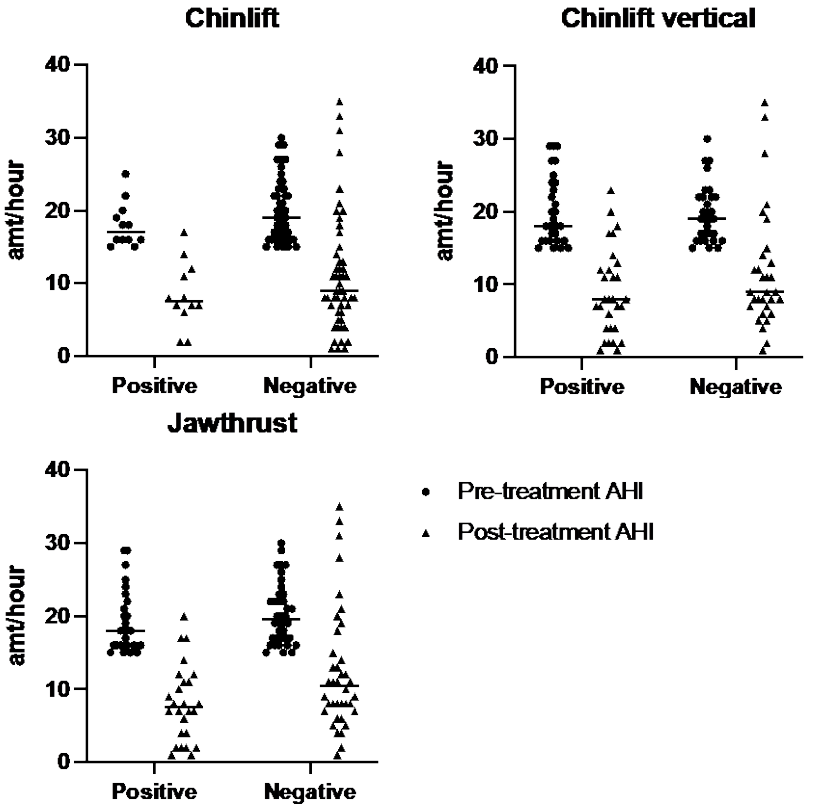

Figure 5.3 Individual pre- and post-treatment AHI. Patients are categorized according to the response to the mandibular advancement maneuvers.

Post-treatment quality of life

The mean post-treatment ESS was 7.6 ± 4.6; the mean post-treatment FOSQ-30 was 98.7 ± 19.2; no significant differences were found between responders and non-responders and deteriorating and non-deteriorating patients.

Complications

44 patients (69%) had no complications. 13 patients (20%) had temporomandibular dysfunction (TMD); 11 patients (17%) had dental pain; 2 patients (3%) had gingival irritation and 2 patients (3%) had dentofacial changes. There were no patients that reported a dry mouth or hypersalivation. There were no differences in complications between responders and non-responders and deteriorating and non-deteriorating patients (Table 5.3).

Table 5.3 Complications.

Complications	Total sample (n=64)
None	44 (69%)
TMD	13 (20%)
Dental pain	11 (17%)
Gingival irritation	2 (3%)
Dry mouth	0 (0%)
Hypersalivation	0 (0%)
Dentofacial changes	2 (3%)

n= Number; TMD= temporomandibular dysfunction.

Linear regression analyses

Linear regression analyses were performed to establish the predictive value of the three different mandibular advancement maneuvers on the post-treatment AHI. Corrections were made for; gender, age, BMI, pre-treatment AHI and the presence of positional OSA. Patients with a positive mandibular advancement maneuver had a lower post-treatment AHI, however only for the jaw thrust maneuver this relationship proved to be statistically significant (chin lift: β=1.98; 95%CI: -2.90; 6.86; p=0.43; chin lift vertical: β=3.49; 95%CI: -0.39; 7.37; p=0.08; jaw thrust: β=4.88; 95%CI: 1.04; 8.73; p=0.01). Similar results were found for the predictive value of the mandibular advancement maneuvers on the post-treatment ODI≥3% (chin lift: β=0.72; 95%CI: -4.26; 5.70; p=0.78; chin lift vertical: β=2.34; 95%CI: -1.73; 6.41; p=0.26; jaw thrust: β= 4.46; 95%CI: 0.48; 8.44; p=0.03). Indicating that a positive jaw thrust maneuver is an independent predictor for favorable OAT response.

Linear regression analyses were performed to establish the predictive value of the level and degree of collapse according to the VOTE classification on the post-treatment sleep study parameters. Corrections were made for; gender, age, BMI, pre-treatment AHI and the presence of positional OSA. No significant relationships were found between the level and degree of collapse according to the VOTE classification and post-treatment sleep study parameters.

Additionally, linear regression analyses were performed to establish the predictive value of the level and degree of persistent collapse in patients with a negative mandibular advancement maneuver. Corrections were made for; gender, age, BMI, pre-treatment AHI and the presence of positional OSA. A significant relationship was found between a persistent lateral oropharyngeal collapse when performing a chin lift maneuver and the post-treatment AHI (β=-13.02; 95% CI: -19.25; -6.79; p<0.001); indicating that a persistent lateral oropharyngeal collapse when performing a chin lift maneuver is a negative predictor for OAT. A similar significant relationship was found between persistent lateral oropharyngeal collapse when performing a vertical chin lift maneuver (β=-15.12; 95% CI: -23.16; -7.1; p<0.001) and a persistent lateral oropharyngeal collapse when performing a jaw thrust maneuver (β=-17.03; 95% CI: -23.14; -10.92; p<0.001). Similar results were found between a persistent lateral oropharyngeal collapse and the post-treatment ODI ≥3%. These relationships remained significant when correction was made for tonsil size. Additionally, a significant relationship was found between a persistent complete concentric collapse (CCC) at the level of the velum when performing a vertical chin lift maneuver and the post-treatment AHI (β=-23.26; 95% CI: -32.46; -14.07; p<0.001). Indicating that a CCC at the level of the velum when performing a vertical chin lift maneuver is a negative predictor for OAT. A similar relationship was found between a persistent CCC at the level of the velum and the post treatment ODI≥3%. However, only two patients had a persistent complete concentric collapse (CCC) at the level of the velum when performing a vertical chin lift maneuver.

Discussion

The key finding of this study is that a positive jaw thrust maneuver is significantly associated with favorable OAT response in patients with moderate OSA, whereas the chin lift maneuver and the vertical chin lift maneuver are not. The β-coefficient in the linear regression analysis indicates that in patients with a positive jaw thrust maneuver there is an average reduction of 4.88 e/h in post-treatment AHI in comparison to patients with a negative jaw thrust maneuver. However, unlike the hypothesis based on

prior retrospective research, a negative jaw thrust maneuver did not prove to be a significant predictor for OAT failure. Nearly 50% of the responder patients was not correctly identified by the jaw thrust maneuver. A second finding is that a persistent lateral oropharyngeal collapse when performing any mandibular advancement maneuver is significantly associated with unfavorable OAT response in patients with OSA. Both were independently associated with OAT response, corrections were made for gender, age, BMI, pre-treatment AHI and the presence of positional OSA. The results of this prospective study are in concordance with what was previously described in literature. However, thus far no prospective study was performed that included patients treated with OAT despite a negative response to the mandibular advancement maneuver, possibly indicating unfavorable OAT response.

Given the large range in response rate, it is important to establish criteria that reliably pre-select patients that may benefit from OAT prior to the initiation of therapy. DISE has been suggested by several authors as potential clinical method for patient selection. However, other authors advocate that DISE is expensive, and patients have to undergo sedation. A recent study by Sutherland et al. concluded that phenotypic awake assessments do not improve the prediction of OAT treatment outcome, beyond models only using clinical characteristics[32]. A review by Cheong et al. concluded that DISE is a low-risk procedure providing an increased understanding of a patient's upper airway to make adequate treatment that may increase the frequency of positive treatment outcome[33]. Nevertheless, the primary objective of a diagnostic tool should be to exclude patients who are expected to be non-responders. Due to the lack of prospective validation regarding the use of a negative jaw thrust maneuver in the current study, uncertainties arise regarding the justification of DISE with mandibular advancement maneuvers solely for predicting efficacy of OAT.

Previously, different authors have retrospectively shown that a mandibular advancement maneuver could be of prognostic value in determining effectiveness of OAT[18,19,22,34]. Other authors have prospectively evaluated treatment effect of OAT with and without prior DISE with mandibular advancement maneuver. They found a significant difference in terms of AHI reduction in favor of the DISE group[25,35]. This is in correspondence with the current study, showing that a positive jaw thrust maneuver is significantly associated with favorable OAT response. Additionally, several authors have performed DISE with a custom-made simulation bite and found that patients with relief of obstruction on all levels had a higher response rate to OAT in comparison with patients with either partial or no relief of obstruction[23,24,36–38]. Furthermore, additional value was found in the quantitative pharyngeal airway measurements during DISE with

OAT in situ in evaluating treatment outcome[39]. These authors advocate that a jaw thrust maneuver is non-reproducible and non-titratable and may overestimate the treatment effect of OAT[23,24,37]. The current study aims to inform clinical practice; a jaw thrust maneuver is less expensive than a custom-made simulation bite and is easy to use in clinical practice. Additionally, a recent study performed DISE with mandibular advancement maneuver and a custom-made simulation bite in situ and found that both modalities are close to mimicking the expected effect on upper-airway obstruction of OAT[40].

Strengths and limitations

This is the first prospective study that treated patients with OAT despite a negative response to the mandibular advancement maneuver, possibly indicating unfavorable OAT response. This is an important strength, because this gives the opportunity to prospectively validate DISE with mandibular advancement maneuvers as a prediction tool for OAT. The linear regression analyses were performed with continuous variables; the post-treatment AHI and the post-treatment ODI≥3%. Whereas, in previous studies, conclusions were based on dichotomous variables; responder versus non-responder. Three different mandibular advancement maneuvers were used to predict success of OAT; the chin lift maneuver and the jaw thrust maneuver are both established in literature as possible predictors for treatment response of OAT. The chin lift maneuver with vertical opening was previously introduced by other authors because the other two maneuvers might not account for the vertical mouth opening that is induced by OAT[23,24,41].

Only patients with moderate OSA (AHI 15 to 30 e/h) were included in this study. This might have introduced a selection bias. This decision was made to avoid unnecessary sleep studies, as moderate OSA patients are typically recommended for follow-up assessments after OAT therapy. Additionally, it is known that in patients with a higher AHI the likelihood of OAT failure is higher, resulting in a smaller study population while still maintaining reasonable power. Furthermore, the default sleep study was a respiratory polygraphy (PG), but a small subset of patients underwent a PSG or HST. Consequently, there is a heterogeneity in the assessment of respiratory parameters due to use of these three different sleep studies. This was the case in the minority of patients and these patients were equally distributed among the responder groups, minimizing the potential bias in the results. However, AHI measurement might be underestimated in a PG or HST due to not considering the time that the patient is awake. Additionally, the assessment of the upper airway during DISE and the mandibular advancement maneuvers are based on subjective findings and, therefore, are prone to experience

bias; a mandibular advancement maneuver cannot be performed exactly similar in every patient. Previous studies have shown DISE to be reliable and its interobserver reliability to be moderate to substantial, especially in experienced ENT surgeons[42–44]. In the present study, all DISE procedures and concomitant mandibular advancement maneuvers were executed by one surgeon (MC). All DISE procedures were recorded and available for later review. All DISE procedures were carried out with a bolus technique, previous literature has shown that this provides less stable and reliable sedation in comparison to the use of propofol with target-controlled infusion (TCI)[45,46]. This can possibly induce higher tolerability to the mandibular advancement maneuver, resulting in an overestimation of the OAT effect explaining for the false positive patients in the non-responder group. Conversely, if patients were not sufficiently sedated it is possible that the jaw thrust maneuver was not executed to adequate extent. This could explain for the false negative patients in the responder group. Additionally, the degree of mandibular advancement of the OAT was titrated subjectively until the maximum comfortable limit was achieved, and subjective complaints were reduced. This approach has been a subject of debate due to its inherent imprecision and subjectivity, potentially accounting for the false positive results observed in the non-responder group, which could be attributed to insufficient titration. A recent study by Kazemeini et al. has evaluated clinical effectiveness of subjective titration versus objectively guided titration during PSG and DISE in OAT for patients with OSA and found no differences in optimal mandibular positioning and corresponding efficacy[47]. Additionally, Ma et al. has shown that OAT reaches a plateau stage after reaching approximately 70% of protrusion, suggesting that more protrusion does not always yield to a decrease in AHI[48].

Conclusion

In this prospective study, the presence of a positive jaw thrust maneuver was significantly associated with favorable OAT response, leading to an average reduction of 4.88 e/h in post-treatment AHI in comparison to patients with a negative jaw thrust maneuver. Additionally, a significant association was found between a persistent lateral oropharyngeal collapse when performing any mandibular advancement maneuver and unfavorable OAT response. Contrary to our initial hypothesis, a negative jaw thrust maneuver did not prove to be a significant predictor for unfavorable response to OAT. Consequently, uncertainties arise regarding the justification of performing DISE solely for predicting OAT efficacy, since the primary objective of a diagnostic tool should be to exclude patients who are expected to be non-responders. However, this study aimed to inform clinical practice, and therefore is limited by heterogeneity in the assessment of

the respiratory parameters due to the use of three different sleep studies, variability in the performance of the mandibular advancement maneuvers and the instability of the sedation due to the usage of bolus technique during DISE instead of TCI. Consequently, future prospective studies should be conducted while considering these constraints.

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Chapter 6

Upper airway stimulation in patients with obstructive sleep apnea: long-term surgical success, respiratory outcomes, and patient experience

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Abstract

Introduction

Upper airway stimulation (UAS) with electric activation of the hypoglossal nerve has emerged as a promising treatment for patients with moderate-to-severe obstructive sleep apnea.

Objective

To retrospectively analyze objective and subjective outcome measures after long-term follow-up in obstructive sleep apnea patients receiving upper airway stimulation.

Methods

An observational retrospective single-center cohort study including a consecutive series of patients diagnosed with obstructive sleep apnea receiving upper airway stimulation.

Results

Twenty-five patients were included. The total median apnea-hypopnea index (AHI) significantly decreased from 37.4 to 8.7 events per hour at the 12-month follow-up (p<0.001). The surgical success rate was 96%. Adverse events were reported by 28% of the patients.

Conclusion

Upper airway stimulation is an effective and safe treatment for obstructive sleep apnea in patients with continuous positive airway pressure (CPAP) failure or intolerance. However, it is possible that the existing in and exclusion criteria for UAS therapy in the Netherlands have positively influenced our results.

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repetitive partial or complete upper airway obstruction which often results in decreased arterial oxygen saturation and arousal from sleep[1]. The current gold standard treatment of moderate-to-severe OSA is continuous positive airway pressure (CPAP)[2]. However, compliance and long-term use of CPAP is rather low[3]. Alternative treatments include custom-made oral appliance therapy (OAT), positional therapy and upper airway surgery. Since evidence-based reviews do not uniformly support the efficacy of these treatments for moderate-to-severe sleep apnea, a new therapy is desirable[4,5]. Upper airway stimulation (UAS) with electric activation of the hypoglossal nerve has emerged as a promising treatment for patients with moderate-to-severe obstructive sleep apnea who have failed CPAP. Upper airway stimulation has shown favorable success and low morbidity[6–9]. The aim of the present study was to retrospectively analyze the single-center results in terms of surgical success, respiratory outcomes, subjective outcome measures, and adverse events (AEs) in patients with OSA treated with upper airway stimulation.

Methods

Study design and population

An observational retrospective single-center cohort study was conducted at the department of otorhinolaryngology in the St. Antonius Hospital. Patients were included in this study if they were diagnosed with OSA and underwent implantation of an upper airway stimulation system. One-year follow-up data had to be available. In the Netherlands, the main inclusion criteria for implantation of UAS are failure of or intolerance to treatment with CPAP, an apnea-hypopnea index (AHI) between 30 and 50 events per hour, including less than 25% central apneas, and a body-mass index (BMI) <32 kg/m^2. The exclusion criteria include a complete concentric collapse at velopharyngeal level objectified during drug-induced sleep endoscopy, severe restrictive or obstructive pulmonary disease, moderate-to-severe pulmonary arterial hypertension, severe valvular heart disease, New York Heart Association class III or IV heart failure, recent myocardial infarction or severe cardiac arrhythmias (within the past 6 months), persistent uncontrolled hypertension despite medical use, active psychiatric disease, coexisting non-respiratory sleep disorders that would confound functional sleep assessment and expected future indications for a magnetic resonance imaging (MRI) scan of the chest or the abdomen.

Upper airway stimulation system

The UAS system (Inspire Medical Systems Inc., Maple Grove, MN) consists of a respiration sensor, programmable implanted pulse generator (IPG), and stimulating electrodes. The sensor is placed between the internal and external intercostal muscles and detects respiratory efforts from chest excursions that are analyzed by the IPG. The IPG is implanted below the clavicle and delivers stimulation synchronized with the respiratory cycle to the stimulation electrode. The stimulation electrode is placed on the anterior branches of the hypoglossal nerve and cervical spinal nerve 1 (C1). Upon stimulation, these nerves cause forward protrusion of the tongue by stimulating the genioglossus muscle. Furthermore, stimulation of C1 causes an anterosuperior displacement of the hyoid bone, both increasing the size of the oropharyngeal airway. Additionally, previous studies have shown that the effect of upper airway stimulation is not limited to the level of the tongue base, but it also improves airway patency at the level of the palate caused by palatoglossal coupling[10,11].

Objective outcome measures

In-laboratory polysomnography (PSG) was performed at baseline in all patients. After implantation of the UAS in-laboratory PSG was performed at 2, 6, and 12 months. Polysomnography included electroencephalography, electrooculography, surface electromyography, nasal airflow, and air temperature, thoracoabdominal movements, pulse oximetry, body position, and snoring sounds. Breathing was recorded with nasal pressure and temperature sensors. Scoring of electronic raw data was performed manually, following the recommendations of the American Academy of Sleep Medicine[12]. Apnea was defined as a decrease of at least 90% of airflow from baseline for >10 seconds. Hypopnea was defined as a decrease of at least 30% of airflow from baseline for >10 seconds, associated with either an arousal or ≥3% arterial oxygen saturation decrease. The mean AHI was calculated. The oxygen desaturation index (ODI) ≥3% was defined as the mean number of arterial oxygen desaturations ≥3% per hour. The ODI ≥4% was defined as the mean number of arterial oxygen desaturations ≥4% per hour. Other PSG parameters collected included the apnea index (AI), the AHI in supine position, the AHI in non-supine position, and mean arterial oxygen saturation (SpO2). Patient therapy use was measured in hours per week and was collected during the in-laboratory PSG. Surgical success was defined according to the Sher criteria: a reduction in baseline AHI of more than 50%, and a postoperative AHI of less than 20 events per hour[13]. An additional classification was made for patients with a reduction in baseline AHI of more than 50% and a postoperative AHI of less than 15 events per hour. Adverse

events were collected at the 6- and 12- month visits and were subdivided into procedure- and therapy-related AEs.

Subjective outcome measures

The Epworth sleepiness scale (ESS), which was designed to assess the extent of daytime sleepiness, was collected at baseline in all patients[14]. Additionally, all patients completed the ESS at 6- and 12-month visit. An adapted clinical global impression (CGI) scale, which was originally designed for patients with mental disorders, was used by the physician to compare the present clinical condition to baseline. The CGI ranges from 1 (very much improved) to 6 (very much worse). Furthermore, all patients received a questionnaire regarding patient experience with therapy (PET). This questionnaire consists of four questions regarding patient satisfaction:

- How does UAS therapy compare against your previous experience with CPAP?
- What is the likelihood of choosing UAS therapy again?
- What is the likelihood of recommending UAS therapy to friends/family?
- Overall, how satisfied are you with UAS therapy?

Ethical considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Data on study subjects were collected and stored anonymously to protect personal information. Informed consent was obtained prior to data collection.

Statistical analysis

The statistical analysis was performed by using the IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). Normally distributed continuous data are presented as means with standard deviations. Non-normally distributed continuous data are presented as median with interquartile range (IQR). Categorical variables are presented as frequencies with percentages. Comparisons between groups were performed using Chi-squared tests for categorical variables, paired t test and Wilcoxon rank sum test for continuous variables. A two-tailed p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

This retrospective analysis consists of 25 patients undergoing implantation of upper airway stimulation between January 2018 and September 2019, baseline characteristics are mentioned in Table 6.1. Ninety-six percent of the patients were male with a mean age of 62.40 ± 9.45 years. The mean body-mass index (BMI) was 28.18 ± 2.34 kg/m^2. The median baseline AHI was 37.40 (33.7–45.6) e/h, with a mean ESS of 10.28 ± 5.26. The median ODI ≥4% was 20.10 (16.5–27.2) e/h. Fourteen patients (56%) previously underwent a tonsillectomy. All other patients had small tonsils, varying from tonsil size 1 to 2. The median Mallampati score was 3.

Table 6.1 Baseline characteristics.

Measurement	n=25
Male patients	24 (96%)
Age (mean ± SD; years)	62.40 ± 9.45
BMI (mean ± SD; kg/m^2)	28.18 ± 2.34
AHI (median (Q1-Q3); e/h)	37.40 (33.7–45.6)
ODI ≥4% (median (Q1-Q3); e/h)	20.10 (16.5–27.2)
ESS (mean ± SD)	10.28 ± 5.26

AHI, apnea-hypopnea index; BMI, body-mass index; ESS, Epworth sleepiness scale; ODI, oxygen desaturation index; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

Objective outcome measures

A complete overview of the objective outcome measures at 6- and 12-month follow-up is shown in Table 6.2. The total median AHI at the 6-month follow-up significantly decreased from 37.40 (33.7–45.6) e/h to 8.10 (3.9–15.0) e/h (p<0.001). Both the median AHI in supine position and non- supine position significantly decreased, from 59.30 (38.4–77.4) e/h to 22.60 (9.6–31.9) e/h and from 25.60 (15.3–27.2) e/h to 5.90 (2.3-12.4) e/h, respectively (p=0.001; p<0.001). The median ODI ≥4% significantly decreased from 20.10 (16.5–27.2) e/h to 4.50 (1.7–7.4) e/h (p<0.001). The mean therapy usage at the 6-month follow-up was 6.96 ± 1.59 hour/night. The median AHI at 12-month follow-up significantly decreased to 8.70 (4.8–12.7) e/h (p<0.001). The median AHI in supine position and non-supine position was 20.70 (12.5–36.9) e/h and 8.40 (2.7-11.3) e/h, respectively (p<0.001; p<0.001). The median ODI ≥4% was 6.00 (5.0–12.6) e/h (p<0.001). The mean therapy usage at 12- month follow-up was 5.83 ± 1.70 hour/night.

Table 6.2 Outcome measures at 6- and 12-month follow-up.

Measurement	Preoperative	Time point	Postoperative	*p*-value
AHI (median (Q1-Q3); e/h)	37.40 (33.7–45.6)	6 months	8.10 (3.9–15.0)	<0.001*
		12 months	8.70 (4.8–12.7)	<0.001*
AI (median (Q1-Q3); e/h)	16.00 (7.6–30.0)	6 months	2.20 (0.9–3.7)	<0.001*
		12 months	3.50 (1.1–5.5)	<0.001*
Supine AHI	59.30 (38.4–77.4)	6 months	22.60 (9.6–31.9)	0.001*
(median (Q1-Q3); e/h)		12 months	20.70 (12.5–36.9)	<0.001*
Non-supine AHI (median (Q1-	25.60 (15.3–27.2)	6 months	5.90 (2.3–12.4)	<0.001*
Q3); e/h)		12 months	8.40 (2.7–11.3)	<0.001*
ODI ≥3%	32.90 (27.9–36.9)	6 months	11.60 (6.8–16.4)	<0.001*
(median (Q1-Q3); e/h)		12 months	14.30 (10.7–25.2)	<0.001*
ODI ≥4%	20.10 (16.5–27.2)	6 months	4.50 (1.7–7.4)	<0.001*
(median (Q1-Q3); e/h)		12 months	6.00 (5.0–12.6)	<0.001*
Mean SpO2 (mean ± SD)	93.91 ± 1.30	6 months	94.08 ± 1.54	0.472**
		12 months	93.71 ± 1.70	0.346**
ESS (mean ± SD)	10.28 ± 5.26	6 months	7.95 ± 2.93	0.007**
		12 months	7.04 ± 3.61	0.002**
Therapy usage (mean ± SD;		6 months	6.96 ± 1.59	-
h/night)		12 months	5.83 ± 1.70	-

AHI, apnea-hypopnea index; AI, apnea-index; BMI, body-mass index; ESS, Epworth sleepiness scale; ODI, oxygen desaturation index; Q1, quartile 1; Q3, quartile 3; SD, standard deviation, SpO2, arterial oxygen saturation. *Wilcoxon signed-rank test. **Paired *t*-test.

Subjective outcome measures

The mean ESS significantly decreased from 10.28 ± 5.26 to 7.95 ± 2.93 and 7.04 ± 3.61 respectively at 6- and 12-month follow-up (p=0.007; p=0.002) (Table 6.2). The summarized data of CGI at 6- and 12-month follow-up is shown in Table 6.3. At the 6-month follow-up, the CGI of 96% of the patients is minimally, much, or very much improved. At the 12-month follow-up, all patients were at least minimally improved in comparison to baseline. Table 6.4 shows the results of the PET questionnaire. At the 6- and 12-month follow-ups, respectively, 84.61% and 69.57% of the patients declared UAS was better than CPAP therapy; 100% and 82.61% would choose UAS again; 84.61% and 73.91% would recommend UAS to friends/family; 92.31% and 69.57% were satisfied with UAS therapy.

Table 6.3 Clinical global impression.

Clinical global impression	6 months	12 months
Very much improved	6 (24%)	11 (47.83%)
Much improved	12 (48%)	8 (43.78%)
Minimally improved	6 (24%)	4 (17.39%)
No change	1 (4%)	0 (0%)
Minimally worse	0 (0%)	0 (0%)
Much worse	0 (0%)	0 (0%)
Very much worse	0 (0%)	0 (0%)

Surgical success

The surgical success rate according to the Sher criteria was 92% at the 6-month follow-up and 96% at the 12-month follow-up. Additionally, at the 6-month follow-up, 76% met the additional criteria of ≥50% reduction from baseline AHI and a postoperative AHI of ≥15. At the 12-month follow-up, 88% had met the additional criteria.

Table 6.4 Patient experience with therapy.

Patient experience with therapy		6 months	12 months
How does your UAS therapy compare against your previous experience with CPAP?	UAS is much better than CPAP	76.92%	65.22%
	UAS is better than CPAP	7.69%	4.35%
	CPAP and UAS are equal	0%	0%
	CPAP is better than UAS	0%	4.35%
	CPAP is much better than UAS	0%	4.35%
	N/A – No experience with CPAP or did not use CPAP long enough	15.38%	21.74%
What is the likelihood of choosing UAS therapy again?	Strongly agree	84.62%	65.22%
	Agree	15.38%	17.39%
	Neither agree nor disagree	0%	8.7%
	Disagree	0%	4.35%
	Strongly disagree	0%	4.35%
What is the likelihood of recommending UAS therapy to friends/family?	Strongly agree	69.23%	43.48%
	Agree	15.38%	30.43%
	Neither agree nor disagree	15.38%	17.39%
	Disagree	0%	8.7%
	Strongly disagree	0%	0%
Overall, how satisfied are you with UAS therapy?	Very satisfied	38.46%	21.74%
	Satisfied	53.85%	47.83%
	Neither satisfied nor dissatisfied	7.69%	21.74%
	Dissatisfied	0%	4.35%
	Very dissatisfied	0%	4.35%

CPAP, continuous positive airway pressure; UAS, upper airway stimulation.

Adverse events

A complete overview of reported AEs is presented in Table 6.5. Nine patients (36%) reported at least one adverse event at the 6-month follow-up. Ten AEs were reported in total, with stimulation-related discomfort being the most common, reported 7 times (28%). Two patients (8%) developed a submental hematoma postoperatively. One patient (4%) developed a postoperative wound infection. At the 12-month follow-up, 7 patients (28%) reported at least one AE, with a total of 8 AEs reported. Three patients (12%) still experienced stimulation-related discomfort. Two patients (8%) experienced tongue abrasion. One patient (4%) experienced dentofacial changes of the lower teeth, and two patients (8%) needed an additional barbed stitch pharyngoplasty due to persistent velopharyngeal collapse as a result of lack of palatoglossal coupling[11]. No severe or irreversible AEs were reported.

Table 6.5 Adverse events.

Time point	Overall AE rate*	Adverse event	Frequency of AE reported				
			Total reported**	Frequency of AE***	Mild****	Moderate****	Severe****
6 Months	9 (36%)	Tongue weakness	10	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Swallowing/speech related AE		0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Discomfort related to incision/scar		0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Discomfort related to IPG		0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Infection		1 (4%)	1 (4%)	0 (0%)	0 (0%)
		Other procedure related AE±		2 (8%)	2 (8%)	0 (0%)	0 (0%)
		Stimulation related discomfort		7 (28%)	7 (28%)	0 (0%)	0 (0%)
		Tongue abrasion		0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Insomnia/arousals		0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Revision intervention		0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Other therapy related AE		0 (0%)	0 (0%)	0 (0%)	0 (0%)
12 Months	7 (28%)	Tongue weakness	8	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Swallowing/speech related AE		0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Discomfort related to incision/scar		0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Discomfort related to IPG		0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Infection		0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Other procedure related AE		0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Stimulation related discomfort		3 (12%)	3 (12%)	0 (0%)	0 (0%)
		Tongue abrasion		2 (8%)	2 (8%)	0 (0%)	0 (0%)
		Insomnia/arousals		0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Revision intervention		0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Other therapy related AE±±		3 (12%)	3 (12%)	0 (0%)	0 (0%)

AE, adverse event; IPG, implanted pulse generator. *This number represents the total number of patients who reported at least one AE; **This number represents the total number of AEs reported at this time point; ***This number represents the number and percent of patients who reported this AE; ****This number represents the number and percent of patients who reported this AE with each severity of the AE reported; ±Two patients developed a submental hematoma postoperatively; ±±One patient experienced dentofacial changes of the lower teeth, two patients needed an additional barbed reposition pharyngoplasty due to lack of palatoglossal coupling.

Discussion

The present study aimed to retrospectively analyze the long- term postoperative outcomes of UAS in patients with moderate to severe OSA with CPAP failure or intolerance. Upper airway stimulation significantly improved respiratory parameters measured by PSG. The overall surgical success rate measured by the Sher criteria was 92% and 96% at the 6- and 12-month follow-ups, respectively. Additionally, there was a significant decrease in ESS measured at the 6- and 12- month follow-ups.

Thaler et al. recently published the results of 382 patients enrolled in the ADHERE upper airway registry[10]. They found a significant reduction in median AHI from 32.8 e/h to 6.3 e/h and 9.5 e/h at the 6- and 12-month follow-ups, respectively. The surgical success rate, according to the Sher criteria, was 85% and 69%, respectively. They found a significant reduction in the median ESS from 11.0 to 7.0 and 6.0, respectively. The mean therapy usage at 12-month follow-up was 5.7 hour/night. Ninety-two percent of investigators reported improvement with treatment after the participant received an UAS system; 93% of participants reported overall satisfaction with UAS treatment; 95% preferred UAS over CPAP; 94% would choose UAS again if asked; and 96% would recommend UAS to family and friends. Adverse events were reported by 46% at the 6-month follow-up and 32% at the 12-month follow-up. Previously, Heiser et al. also published results of the ADHERE upper airway registry[9]. Reporting on 508 patients, the median AHI decreased from 34.0 e/h to 5.7 e/h and 7.0 e/h, respectively, at the posttitration and the final follow-up visits. The surgical success rate, according to the Sher criteria, was 92% and 81%, respectively. The mean ESS decreased significantly from 11.8 to 7.7 and 6.7, respectively. Ninety-four percent of physicians rated improvement on the CGI, which persisted in 93% at the final visit. Ninety-six percent of the subjects reported that UAS was better than CPAP therapy post-titration and at the final follow-up visit; 95% stated that they would undergo UAS again at the post-titration visit; and 94% at the final follow-up visit. Ninety-three percent reported that they would recommend UAS to family and friends, which increased to 96% at the final follow-up visit. Ninety-one percent reported that, overall, they were satisfied with UAS therapy at the post-titration visit, and 94% at the final follow-up visit. Boon et al. also reported on the ADHERE upper airway registry and reported similar outcomes to those of Thaler et al. and Heiser et al.[7] Mehra et al. recently published a parallel arm study design to compare objective sleep apnea measures, and patients reported outcomes in those who received UAS approval versus denial in a multinational prospective study[15]. In 250 patients treated with UAS, they found a significant reduction in median AHI from 31.3 e/h to 10.1 e/h at the 12-month follow-up. There was a significant decrease in the mean ESS from 13.0 to 6.0. Freedom from procedure-related AEs was present in 97% of those who underwent UAS. Freedom of therapy-related AEs was present in 90%. Woodson et al. reported 5-year outcomes of patients receiving UAS therapy. They reported a surgical success measured by the Sher criteria of 75%. The responder rate at the 5-year follow-up was 63%[8]. Earlier, Strollo et al. found a significant reduction in AHI from 29.3 e/h to 9.0 e/h and ODI from 25.4 to 7.4 e/h in moderate-to-severe OSA patients 12-months after implantation, with a surgical success rate of 66%[6]. The mean ESS significantly decreased from 11.6 to 7.0.

In comparison to previously published studies, the baseline AHI was higher in our patient population. This can be explained by the fact that, in the Netherlands, costs for

treatment with UAS are only reimbursed for patients with an AHI between 30 and 50 e/h, while in most other countries the inclusion range is 15 to 65 e/h. The postoperative AHI was similar to those of earlier studies, indicating that the reduction in AHI is larger than in previous studies. The surgical success rate according to the Sher criteria was also higher than in previous studies. The reduction in ESS and the CGI was similar to what was mentioned by previous authors. The answers to the PET questionnaire were less positive in this cohort in comparison to previous descriptions of larger cohorts. A possible explanation can be that the two patients who received an additional barbed reposition pharyngoplasty due to lack of palatoglossal coupling were dissatisfied due to the fact that they needed additional surgery. This has largely influenced the results due to the small sample size. The adverse event rate was similar to the AE rate mentioned by Thaler et al.[10] However, Mehra et al. reported a lower AE rate[15]. In this cohort, no severe or irreversible AEs were reported. Stimulation-related discomfort was the most common AE reported. This is generally a short-term problem, and most patients do not experience discomfort after an intensive titration period.

In the present cohort, the AHI in non-supine position showed a larger decrease in comparison to baseline than the AHI in supine position. A possible explanation for this is that in our experience during in-laboratory titration visits, in supine position a higher stimulation level is needed than in non-supine position. However, this stimulation level is often not tolerated by the patients, causing discomfort and waking them up at night, forcing them to lower the stimulation themselves. This is probably the reason why the AHI in non-supine position shows a larger decrease than the AHI in supine position.

It is notable that, at the 12-month follow-up, the success rate according to the Sher criteria was higher than the success rate at the 6-month follow-up. This indicates that long and intensive follow-up shows improvement of respiratory parameters. The ESS was also lower at the 12-month follow-up, indicating that patients experienced less OSA-related complaints. In contrast, the answers to the PET questionnaire were less positive at the 12-month follow-up. A possible explanation can be that the two patients who received an additional barbed reposition pharyngoplasty due to lack of palatoglossal coupling were dissatisfied due to the fact that they needed additional surgery. Preoperative screening measures are needed to identify patients without palatoglossal coupling. Additionally, not all patients are aware of the intensive titration that is needed in the first year after implantation. Further counseling and intensive follow-up are needed to maintain favorable results.

Clinical relevance

Obstructive sleep apnea is associated with cardiovascular and metabolic consequences and is alsolinked with increased overall mortality[16]. Therefore, in patients with moderate-to-severe

OSA and CPAP failure or intolerance, alternative treatment options are important. In this patient cohort in the Netherlands, UAS shows a high surgical success rate with no severe or irreversible AEs. This is similar to the results of previous studies in other countries. Therefore, UAS is an effective and safe alternative in patients with CPAP failure or intolerance.

Limitations and strengths

The present study is not without limitations. In the Netherlands, the inclusion criteria for UAS include a BMI<32, whereas, worldwide, the inclusion criteria range up to a BMI of 35. Additionally, patients with a complete concentric collapse at the velopharyngeal level were excluded. It is possible that this introduces a selection bias that has positively influenced our results. However, a complete concentric collapse at the velopharyngeal level is currently globally used as an exclusion criterion. Additionally, the results represent the experience of one center. The small sample size of this study is a limiting factor. The published series from Amsterdam, by Vonk et al., describes a larger cohort[17]. However, this is the first study conducted in the Netherlands that reports on long-term follow-up results. Additionally, both objective and subjective outcome measures are reported as well as therapy usage. All patients were followed-up with PSG, whereas, in previous studies reporting on the ADHERE registry, the AHI was based on both PSG and home sleep tests.

Conclusion

Upper airway stimulation proved to be a safe and effective treatment for OSA in patients with CPAP failure or intolerance, with a surgical success rate of 96%. Overall patient satisfaction was high, and no severe or irreversible AEs were reported. However, it is possible that the existing in and exclusion criteria for UAS therapy in the Netherlands have positively influenced our results.

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Chapter 7

Summary, general discussion and future perspectives

Summary, general discussion and future perspectives

The general aim of this thesis was to identify predictors for patients at high risk for obstructive sleep apnea (OSA) and to find independent variables that can predict treatment outcome in patients with OSA. This is important, as is contributes to a better understanding of the clinical presentation of OSA and improves patient-specific treatment planning.

Predictors for patients at high risk for OSA

Currently, overnight polysomnography (PSG) is the gold standard for diagnosing the presence and severity of OSA. However, its high expense, relative inaccessibility, and time consumption can delay or impede the diagnosis and treatment of patients with OSA, mainly in areas with limited healthcare resources. Additionally, the increasing number of patients suspected of having OSA and the lack of structured patient interviews contribute to the growing number of patients being referred to sleep clinics. Therefore, simple screening instruments for identifying patients at high risk for OSA have become increasingly important. In Chapter 2 the performance of the NoSAS score, the STOP-Bang questionnaire, and the ESS as a screening tool for OSA severity was retrospectively evaluated. The severity of OSA was categorized into mild, moderate, and severe based on both the apnea-hypopnea index (AHI) and the oxygen desaturation index (ODI). The NoSAS score and the STOP-Bang questionnaire were equally adequate to detect OSA severity with an area under the ROC curve (AUC) ranging from 0.695 to 0.767 and 0.684 to 0.767, respectively for different degrees of OSA severity. However, due to the low specificity and positive predictive value (PPV) of the STOP-Bang questionnaire, it is possible that the STOP-Bang questionnaire will yield a large proportion of false-positive cases and therefore increase the number of unnecessary nocturnal recordings, whereas the NoSAS score has a higher specificity and PPV, while maintaining a moderate to high sensitivity. Both the NoSAS score, and the STOP-Bang questionnaire perform better when used as a continuous variable, rather than as a dichotomous variable with a cut-off value. However, only for the STOP-Bang questionnaire the difference between using a continuous score and a dichotomous score proved to be significant. The ESS showed poor discrimination for screening for OSA, with an AUC ranging from 0.450 to 0.525. Male gender, age, and body mass index (BMI) proved to be the strongest individual predictors for OSA severity. It is possible that a selection bias was introduced in this study since the questionnaire was applied only to suspected individuals. The great prevalence of OSA in this study population could affect

the interpretation of the screening instruments. Therefore, in future studies are needed in control population cohorts to validate the NoSAS score and the STOP-Bang questionnaire as screening tools for OSA severity. Additionally, there is growing attention to the use of home sleep testing and wearables to detect OSA[1–3]. In the future, this might introduce possibilities to make adequate OSA screening easier, cheaper and less time consuming. Despite these recent advancements in diagnostic methods, screening tools will maintain their significance in identifying patients at high risk for OSA, especially during preoperative assessments, considering the elevated risk of (respiratory) complications during surgical procedures in patients with OSA. In future investigations, it may be valuable to explore whether the screening instruments can not only predict OSA severity, but also assess their potential in anticipating perioperative (respiratory) complications.

Predictors for treatment outcome of CPAP

Continuous positive airway pressure (CPAP) is unequivocally regarded as the gold standard treatment and often the treatment of first choice in patients with moderate to severe OSA. CPAP therapy is known for its high efficacy in reducing the AHI. However, its effectiveness can be limited by adherence and tolerance. Multiple studies have been performed to identify factors that influence or predict CPAP intolerance or non-adherence. However, not much is known about CPAP failure. In **Chapter 3** drug-induced sleep endoscopy (DISE) while administrating CPAP therapy was performed to identify potential causes for CPAP failure. Patients were included if they experienced persistent OSA-related complaints and repeatedly measured an AHI above 5 apneas per hour despite intensive support and additional CPAP titration. This study shows that the possible reason for CPAP failure can predominantly be identified by DISE while administrating CPAP therapy and recommendations for other or additional therapies can be made. Consequently, evidence was found that a lateral oropharyngeal collapse might be a positive predictor for CPAP therapy, while a complete circular collapse at the level of the palate, laryngeal collapse, and epiglottal collapse (i.e., floppy epiglottis) might be negative predictors for CPAP therapy. Notably, several patients with a floppy epiglottis during CPAP treatment were satisfied with CPAP for many years. This raises the question if this phenomenon might be instigated by long-term CPAP usage. Other research groups conducted subsequent studies that yielded comparable findings, indicating that CPAP significantly increases cross-sectional dimensions of the soft palate, lateral walls, and tongue base, but not of the epiglottis. They describe that the epiglottis may become lax and susceptible to collapse when exposed to positive pressure. However, they observed

that epiglottal collapse does not seem to hamper the effectiveness of CPAP improving inspiratory flow. Nevertheless, epiglottal collapse may cause discomfort, and thereby reduce adherence[4]. Both our study and the subsequent study are limited in sample size. Further research with large sample sizes and in patients with different duration of CPAP treatment is needed.

Predictors for treatment outcome of OAT

In patients with mild to moderate OSA or in cases of CPAP intolerance or failure, other treatment options include oral appliance treatment (OAT). While OAT has lower efficacy than CPAP in terms of reducing the AHI, OAT has a higher compliance rate and higher patient preference with fewer side effects, resulting in a similar overall therapeutic effectiveness in patients with mild to moderate OSA[5–8]. Response rate to OAT is patient dependent and is determined by how treatment success is defined. Therefore, it is important to establish criteria that reliably preselect patients that may benefit from OAT prior to the initiation of therapy. Additionally, the majority of OAT is custom-made. Consequently, in case of ineffectiveness, there is a large delay in appropriate treatment and a waste of healthcare supplies. Previous studies have shown increased response to OAT for patients who are young and female, patients with a lower AHI, a lower BMI and supine dependent OSA[9]. Additionally, different polysomnographic endotypes have been associated with OAT efficacy; lower loop gain, higher arousal threshold, lower ventilatory response and less severe airway collapsibility were all found to be independently associated with favorable OAT response[10–12]. DISE is widely recognized as a valuable tool to assess the degree, level, and configuration of upper airway obstruction in patients with OSA, particularly for those who are potential candidates for upper airway surgery or upper airway stimulation. However, the use of DISE in the evaluation of non-surgical interventions, such as OAT, is less well established. Previous authors have advocated that a mandibular advancement maneuver during DISE to mimic the effect of OAT, could be predictive for treatment success[13–16]. However, opinions concerning the performance of a mandibular advancement maneuver vary among studies and evidence on the positive and negative predictive values are so far limited[15,17–21]. In **Chapter 4** the predictive value of DISE with a concomitant jaw thrust maneuver for treatment success of OAT was retrospectively evaluated. Patients were included if they were previously treated with OAT, and subsequently categorized into OAT failure and OAT benefit groups, depending on their prior response to treatment. In all patients DISE with jaw thrust maneuver was performed. The jaw thrust maneuver was called positive if the obstruction was discontinued on all levels and negative if the obstruction was still

present on one or more levels. A negative response to the jaw thrust maneuver was able to predict OAT failure with a negative predictive value (NPV) of 0.88 and a specificity of 0.74. However, a positive jaw thrust maneuver failed to identify nearly half of the responders with a PPV of 0.54. Due to significant differences in the baseline characteristics, a subanalysis was performed in patients with OAT failure and an AHI below 30. In this subanalysis, the jaw thrust maneuver was able to predict OAT failure with a NPV of 0.80, while maintaining a moderate PPV of 0.71. This retrospective data suggests that a negative jaw thrust maneuver during DISE can be a valuable predictor for OAT failure. Additionally, evidence was found that previous tonsillectomy is a predictor for OAT benefit. Based on the results of **Chapter 4**, in **Chapter 5** predictors during DISE for treatment success of OAT were prospectively validated. Patients with moderate OSA were prospectively recruited and underwent DISE with three mandibular advancement maneuvers to predict treatment success of OAT: the chin lift maneuver, the jaw thrust maneuver, and the chin lift vertical maneuver. All patients were treated with OAT and completed a follow-up sleep study with OAT in situ, without regard to their anticipated response to treatment. A positive jaw thrust maneuver was significantly associated with favorable OAT response, leading to an average reduction of 4.88 e/h in post-treatment AHI in comparison to patients with a negative jaw thrust maneuver. Additionally, a significant association was found between a persistent lateral oropharyngeal collapse when performing any mandibular advancement maneuver and unfavorable OAT response. However, in contrast to the findings in **Chapter 4**, a negative jaw thrust maneuver did not prove to be a significant predictor for unfavorable response to OAT. To improve patient-specific treatment outcomes and cost-effectiveness, the primary objective of a diagnostic tool should be to exclude patients who are expected to be non-responders. Consequently, based on this prospective study uncertainties arise regarding the justification of performing DISE solely for predicting the efficacy of OAT. If DISE is already considered for alternative reasons such as surgical planning, the jaw thrust maneuver should be preferred over the chin lift maneuver for predicting OAT response. Patients with a positive jaw thrust maneuver should be counseled towards favorable OAT response, whereas those with persistent lateral collapse should be advised about the likelihood of unfavorable OAT response. This study aimed to inform clinical practice, and therefore is limited by heterogeneity in the assessment of the respiratory parameters, variability in the performance of mandibular advancement maneuvers and the instability of the sedation due to the usage of bolus technique anesthesia. Consequently, future prospective studies should be conducted while considering these constraints.

Predictors for treatment outcome of UAS

Upper airway stimulation (UAS) with electric activation of the hypoglossal nerve has emerged as a promising treatment for patients with moderate to severe OSA who have failed CPAP therapy. In Chapter 6, the long-term postoperative outcomes of UAS in patients with moderate to severe OSA were retrospectively analyzed. UAS significantly improved respiratory parameters as measured by PSG. The overall surgical success rate according to the Sher criteria was 92% and 95% at 6- and 12-month follow-up respectively. Additionally, there was a significant decrease in ESS measured at the 6- and 12-month follow-up visits. There were no severe or irreversible adverse events. In this small retrospective study, significantly poorer outcomes were seen in two patients, which were attributed to a persistent velopharyngeal collapse due to lack of palatoglossal coupling. As a result, both patients required additional barbed reposition pharyngoplasty (BRP). Prior studies have shown that lack of palatoglossal coupling might be a negative predictor for success of UAS, and that additional soft palate surgery might be needed in this patient group[22]. Recent research evaluating mandibular advancement maneuvers during DISE to predict palatoglossal coupling have found them not to be predictive of AHI change[23]. This introduces perspectives for future research into identifying predictors for the absence of palatoglossal coupling to improve patient selection and treatment outcomes in UAS.

In conclusion, this thesis provides important insights into recognizing patients at high risk for OSA and predicting treatment outcomes for different OSA therapies. We advocate that DISE can offer valuable insights for surgical treatment planning and may also be feasible for non-surgical interventions. Additionally, DISE can be a useful tool to establish the reason for failure of non-surgical therapy. However, due to the lack of a prospective validation regarding the use of a negative jaw thrust maneuver to accurately identify non-responders to OAT in the current study, uncertainties arise regarding the justification of performing DISE solely for predicting the efficacy of OAT. The positive jaw thrust maneuver observed during DISE may serve as a predictive tool for OAT if DISE is already conducted for other purposes.

Identifying individual predictors for treatment outcomes can lead to tailored therapeutic approaches, ensuring higher adherence rates and better patient satisfaction. Future research efforts should focus on validating and refining these predictors through prospective studies in larger patient groups, which can ultimately improve the management and treatment of OSA patients. Additionally, there is increasing evidence that simplified metrics like the AHI and the ODI may not adequately express OSA severity

and may not align with patients' self-reported symptoms. Currently, the question arises as to whether determining OSA severity and treatment planning should rely solely on AHI or ODI measurements or if patients' self-reported complaints should be taken into consideration. However, there is still need for an objective measurement that can accurately assess disease severity. Consequently, increasing focus is being directed towards the exploration of biomarkers associated with OSA, which could potentially contribute to the screening and monitoring of OSA.

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Chapter 8

Nederlandse samenvatting

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Het primaire doel van dit proefschrift was het identificeren van factoren die voorspellen welke patiënten een hoog risico op obstructief slaapapneu (OSA) hebben en het vinden van onafhankelijke variabelen die de behandelingsresultaten kunnen voorspellen bij patiënten met OSA. Dit is belangrijk, omdat het bijdraagt aan een beter begrip van de klinische presentatie van OSA en het de planning van op maat gemaakte behandelingen voor individuele patiënten verbetert.

Voorspellers voor patiënten met een hoog risico op OSA

Een polysomnografie (PSG) gedurende de nacht is de gouden standaard voor het diagnosticeren van de aanwezigheid en ernst van OSA. Echter, de hoge kosten, beperkte toegankelijkheid en tijdsbeslag van een PSG kunnen de diagnose vertragen of bemoeilijken, vooral in gebieden met beperkte mogelijkheden. Daarnaast leidt het groeiende aantal patiënten dat verdacht wordt van OSA en het gebrek aan gestructureerde OSA gerichte anamneses tot een groeiend aantal patiënten dat wordt doorverwezen naar slaapklinieken. Eenvoudige screeningsinstrumenten om patiënten met een hoog risico op OSA te identificeren zijn daarom steeds belangrijker geworden. In Hoofdstuk 2 werd er retrospectief gekeken naar de prestaties van de NoSAS-score, de STOP-Bang vragenlijst en de ESS als screeningsinstrument voor de ernst van OSA. De ernst van OSA werd gecategoriseerd als mild, matig of ernstig op basis van zowel de apneu-hypopneu index (AHI), als de zuurstof-desaturatie index (ODI). De NoSAS-score en de STOP-Bang vragenlijst bleken beiden even geschikt om patiënten te herkennen met hoog risico op OSA, met een 'area under the ROC-curve' (AUC) variërend van 0,695 tot 0,767 en 0,684 tot 0,767 voor verschillende mate van OSA. Door de lage specificiteit en positief voorspellende waarde (PVW) van de STOP-Bang questionnaire is het mogelijk dat deze vragenlijst veel vals-positieve patiënten zal identificeren, waardoor er mogelijk veel onnodige slaaponderzoeken zullen plaatsvinden. De NoSAS score heeft daarentegen een hogere specificiteit en PVW, met een gemiddelde sensitiviteit. Beide vragenlijsten presteren beter wanneer ze als continue variabelen worden gebruikt, dan wanneer ze als dichotome variabelen met afkapwaarde worden gebruikt. Hoewel dit verschil alleen in het geval van de STOP-Bang vragenlijst significant bleek. De ESS bleek niet geschikt om te screenen voor OSA, met een AUC van 0.450 tot 0.525. Mannelijk geslacht, leeftijd en 'body mass index' (BMI) bleken de sterkste individuele voorspellers te zijn. Het is mogelijk dat er sprake is van een selectiebias in deze studie, doordat de screeningsinstrumenten enkel zijn toegepast op patiënten die reeds verdacht werden

van OSA. De hoge prevalentie van OSA in de studie populatie kan de interpretatie van de screeninginstrumenten hebben beïnvloed. Toekomstige prospectieve studies dienen uitgevoerd te worden in controlegroepen om de NoSAS score en de STOP-Bang vragenlijst te valideren als screeningsinstrument voor OSA. Daarnaast is er steeds meer aandacht voor het gebruik van thuis-slaaptesten en zogenaamde 'wearables' om OSA op te sporen[1–3]. In de toekomst zou dit mogelijkheden kunnen bieden om adequate OSA-screening gemakkelijker, goedkoper en minder tijdsintensief te maken. Ondanks deze recente ontwikkelingen zullen screeningsinstrumenten van belang blijven om patiënten met een hoog risico op OSA te identificeren, met name tijdens preoperatieve screening, gezien het verhoogde risico op respiratoire complicaties tijdens chirurgische ingrepen bij patiënten met OSA. In toekomstige studies zou het mogelijk relevant kunnen zijn om de waarde van screeningsinstrumenten te onderzoeken voor het voorspellen van perioperatieve complicaties.

Voorspellers voor behandelingsresultaten van CPAP

'Continuous positive airway pressure' (CPAP) wordt beschouwd als de gouden standaard en is vaak eerste behandelingskeuze bij patiënten met matige tot ernstige OSA. CPAP-therapie staat bekend om zijn hoge effectiviteit. Deze effectiviteit wordt echter vaak beperkt door gebrek aan therapietrouw en tolerantie. Er zijn meerdere studies uitgevoerd om factoren te identificeren die CPAP-intolerantie of therapieontrouw beïnvloeden. Er is echter niet veel bekend over CPAP-falen. In Hoofdstuk 3 werd 'drug-induced sleep endoscopy' (DISE) uitgevoerd terwijl CPAP-therapie werd toegepast om mogelijke oorzaken voor CPAP-falen te identificeren. Patiënten werden geïncludeerd als ze persisterende OSA-gerelateerde klachten ondervonden en er herhaaldelijk een AHI boven 5 per uur werd gemeten, ondanks intensieve begeleiding en aanvullende CPAP-titratie. Deze studie toont aan dat de mogelijke reden voor CPAP-falen met dit onderzoek veelal adequaat kan worden geïdentificeerd en dat er aanbevelingen kunnen worden gedaan voor andere of aanvullende therapieën. Daarnaast werd er bewijs gevonden dat laterale orofaryngeale collaps mogelijk een positieve voorspeller is voor CPAP-therapie, terwijl een volledige circulaire collaps op het niveau van het gehemelte, een laryngeale collaps en een collaps van de epiglottis ('floppy' epiglottis) mogelijke negatieve voorspellers zijn. Opmerkelijk is dat meerdere patiënten met een 'floppy' epiglottis eerder jarenlang tevreden waren over de CPAP-behandeling. Dit werpt de vraag op of dit fenomeen veroorzaakt wordt door langdurig CPAP gebruik. Andere onderzoeksgroepen hebben studies uitgevoerd met vergelijkbare resultaten, waaruit blijkt dat CPAP de collaps op het niveau van het zachte gehemelte, de laterale orofarynx

en de tongbasis kan opheffen, maar niet de collaps op het niveau van de epiglottis. Zij beschrijven dat de epiglottis mogelijk slap wordt en gevoelig voor inzakking bij blootstelling aan positieve druk. Zij zagen echter geen afname van effectiviteit van CPAP bij patiënten met collaps van de epiglottis. Desalniettemin kan epiglottis collaps ongemak veroorzaken en daardoor de therapietrouw verminderen[4]. Zowel onze studie als de daaropvolgende studie hebben een beperkte steekproefgrootte. Verder onderzoek met grotere steekproefgroottes en patiënten met verschillende duur van CPAP-behandeling is nodig.

Voorspellers voor behandelingsresultaten met MRA

Bij patiënten met milde tot matige OSA of in het geval van CPAP-intolerantie of -falen behoort behandeling met behulp van een mandibulair repositie apparaat (MRA) tot de overige behandelmogelijkheden. Hoewel behandeling met een MRA een lagere effectiviteit heeft dan CPAP in het verlagen van de AHI, heeft behandeling middels een MRA een hogere therapietrouw, een grotere voorkeur van patiënten en minder bijwerkingen. Dit resulteert in een vergelijkbare algehele therapeutische effectiviteit bij patiënten met milde tot matige OSA[5–8]. Het responspercentage van een MRA is patiënt afhankelijk en hangt af van de definitie van behandelingssucces. Daarom is het belangrijk om criteria vast te stellen die op betrouwbare wijze patiënten kunnen selecteren die zouden kunnen profiteren van een MRA vóór aanvang van de therapie. Als de MRA niet effectief blijkt te zijn, ontstaat er uitstel van adequate behandeling en worden er medische hulpmiddelen verspild, gezien het merendeel van de MRA's op maat gemaakt worden. Eerdere studies hebben aangetoond dat de respons op MRA-therapie hoger is bij patiënten die jong en vrouw zijn, patiënten met een lagere AHI, patiënten met een lagere BMI en patiënten met positioneel slaapapneu[9]. Daarnaast zijn er verschillende endotypes die onderscheiden kunnen worden tijdens een PSG die geassocieerd worden met een hogere werkzaamheid van MRA-therapie, waaronder een lagere 'loop gain', een hogere 'arousal treshold', lagere ventilatoire respons en minder ernstige collaps-neiging van de luchtwegen. Deze factoren zijn allemaal onafhankelijk geassocieerd met een gunstige respons op MRA-therapie[10–12]. DISE wordt algemeen erkend als waardevol hulpmiddel om de mate, het niveau en de configuratie van bovenste luchtwegobstructie te beoordelen bij patiënten met OSA, met name voor potentiële kandidaten voor bovenste luchtwegchirurgie of nervus hypoglossus stimulatie. Het gebruik van DISE bij de evaluatie van niet-chirurgische interventies, zoals MRA-therapie, is echter minder goed vastgesteld. Eerdere auteurs hebben beschreven dat het uitvoeren van een voorwaartse beweging van de onderkaak tijdens DISE om het effect van een MRA na te

bootsen, voorspellend zou zijn voor behandelsucces[13–16]. Echter, de meningen over de uitvoering van deze manoeuvre verschillen tussen de diverse studies en het bewijs over de positieve en negatieve voorspellende waarden hiervan is tot nu toe beperkt[15,17–21]. In Hoofdstuk 4 werd de voorspellende waarde van DISE met gelijktijdige voorwaartse beweging van de onderkaak ('jaw thrust' manoeuvre) voor effectiviteit van MRA-therapie bij patiënten met OSA retrospectief geëvalueerd. Patiënten werden geïncludeerd als ze eerder behandeld waren met een MRA en werden vervolgens ingedeeld in een groep met MRA-falen en een groep met MRA-werkzaamheid afhankelijk van hun eerdere reactie op behandeling. Bij alle patiënten werd een DISE met 'jaw thrust' manoeuvre uitgevoerd. De 'jaw thrust' manoeuvre werd positief genoemd als de obstructie op alle niveaus werd opgeheven en negatief als de obstructie nog aanwezig was op één of meerdere niveaus. Een negatieve 'jaw thrust' manoeuvre kon MRA-falen voorspellen met een negatief voorspellende waarde (NVW) van 0,88 en een specificiteit van 0,74. Een positieve 'jaw thrust' manoeuvre bleek echter onvoldoende geschikt om MRA-werkzaamheid te voorspellen met en positief voorspellende waarde (PVW) van 0,54. Vanwege significante verschillen in de baseline karakteristieken werd een subanalyse uitgevoerd waarbij patiënten met MRA-falen en een AHI onder de 30 vergeleken werden met patiënten met MRA-werkzaamheid. In deze subanalyse bleek de 'jaw thrust' manoeuvre een onafhankelijke voorspeller te zijn met een NVW van 0,80 en een PVW van 0,71. Deze retrospectieve gegevens suggereren dat een negatieve 'jaw thrust' manoeuvre gedurende DISE een waardevolle voorspeller kan zijn voor MRA-falen. Daarnaast werd er bewijs gevonden dat een eerdere tonsillectomie een voorspeller is voor MRA-werkzaamheid. Op basis van de resultaten uit Hoofdstuk 4 werden in Hoofdstuk 5 de mogelijke voorspellers tijdens DISE voor de respons op MRA-therapie prospectief gevalideerd. Patiënten met matig OSA werden prospectief geïncludeerd en ondergingen een DISE met drie verschillende voorwaartse bewegingen van de onderkaak om het behandelsucces van MRA-therapie te voorspellen: de 'chin lift' manoeuvre, de 'jaw thrust' manoeuvre en de 'chin lift' met verticale opening. Alle patiënten werden vervolgens behandeld met een MRA en ondergingen een follow-up slaaponderzoek met MRA in situ, ongeacht hun verwachte reactie op behandeling. Een positieve 'jaw thrust' manoeuvre bleek significant gecorreleerd te zijn met een gunstige respons op MRA-therapie. Patiënten met een positieve 'jaw thrust' manoeuvre hadden gemiddeld een 4,88 e/h lagere AHI na behandeling dan de patiënten met een negatieve 'jaw thrust' manoeuvre. Daarnaast werd er een significante associatie gevonden tussen een persisterende laterale collaps van de orofarynx bij het uitvoeren van elke voorwaartse beweging van de onderkaak en MRA-falen. In tegenstelling tot de bevindingen in Hoofdstuk 4 bleek een negatieve 'jaw thrust' manoeuvre geen significante voorspeller te zijn voor MRA-falen. Om de behandeluitkomsten en

kosteneffectiviteit te verbeteren, moet het primaire doel van een diagnostisch hulpmiddel zijn om patiënten uit te sluiten bij wie therapie falen wordt verwacht. Hierdoor bestaat er in deze prospectieve studie twijfel over de rechtvaardiging van het uitvoeren van een DISE enkel om de effectiviteit van MRA-therapie te voorspellen. Indien DISE reeds wordt overwogen om andere redenen, zoals chirurgische planning, dan verdient de 'jaw thrust' manoeuvre de voorkeur boven de 'chin lift' manoeuvre om MRA-effectiviteit te voorspellen. Patiënten met een positieve 'jaw thrust' manoeuvre moeten worden aangeraden dat een MRA gunstig effect kan hebben, terwijl degene met een persisterende collaps op het niveau van de orofarynx moeten worden geïnformeerd over de waarschijnlijkheid van MRA-falen. Deze studie heeft een aantal beperkende factoren door de heterogeniteit in slaapstudies, de variabiliteit van de voorwaartse manoeuvres van de onderkaak en de instabiliteit van de narcose door het gebruik van bolus techniek. Deze factoren dienen in toekomstig onderzoek meegenomen te worden.

Voorspellers voor behandelingsresultaten met NHS

Nervus hypoglossus stimulatie (NHS) met elektrische activatie van de nervus hypoglossus is een nieuwe veelbelovende behandeling voor patiënten met matige tot ernstige OSA die geen baat hebben gehad van CPAP-therapie. In Hoofdstuk 6 worden de lange termijn resultaten na NHS bij patiënten met matige tot ernstige OSA retrospectief geanalyseerd. NHS verbeterde de parameters gemeten middels PSG significant. Het gemiddelde chirurgische succespercentage volgens de Sher criteria was 92% en 95% na respectievelijk 6- en 12 maanden follow-up. Daarnaast was er een significante afname van de ESS-score gemeten tijdens de follow-up bezoeken na 6- en 12 maanden. Er waren geen ernstige of onomkeerbare complicaties. In deze kleine retrospectieve studie waren twee patiënten met significant slechtere uitkomsten. Deze werden toegeschreven aan het feit dat zij persisterende collaps hadden op het niveau van het zachte gehemelte als gevolg van een gebrek aan koppeling tussen de tong en het gehemelte. Hierdoor hadden beide patiënten een aanvullende 'barbed reposition faryngoplastiek' (BRP) van het gehemelte nodig. Eerdere studies hebben aangetoond dat een gebrek aan koppeling tussen de tong en het gehemelte een negatieve voorspeller kan zijn voor NHS en dat aanvullende operaties aan het gehemelte nodig kunnen zijn bij deze groep patiënten[22]. Recente studies hebben aangetoond dat een 'jaw thrust' manoeuvre tijdens DISE niet voorspellend is voor de koppeling tussen de tong en het gehemelte bij NHS en de effectiviteit op de AHI[23]. Toekomstige studies dienen gericht te zijn op het identificeren van voorspellers voor het ontbreken van koppeling tussen de tong en het gehemelte om de patiënte selectie en behandelingsresultaten van NHS te verbeteren.

Concluderend biedt dit proefschrift waardevolle inzichten in het herkennen van patiënten met een hoog risico op OSA en het voorspellen van behandelingsresultaten voor verschillende OSA-therapieën. DISE met 'jaw thrust' manoeuvre kan waardevolle inzichten bieden, niet alleen voor de planning van chirurgische behandelingen, maar ook voor niet-chirurgische interventies. Bovendien kan DISE een nuttig hulpmiddel zijn om de reden voor falen bij niet-chirurgische therapieën vast te stellen. Echter, vanwege het gebrek aan een prospectieve validatie met betrekking tot de waarde van een negatieve 'jaw thrust' manoeuvre om MRA-falen te voorspellen in de huidige studie, ontstaat er twijfel over het uitvoeren van een DISE enkel en alleen om MRA-werkzaamheid te voorspellen. Een positieve 'jaw thrust' manoeuvre kan dienen als een hulpmiddel om MRA-werkzaamheid te voorspellen indien een DISE al wordt uitgevoerd door andere doeleinden.

Het identificeren van individuele voorspellers voor behandelingsresultaten kan leiden tot op maat gemaakte therapeutische benaderingen, wat zorgt voor hogere therapietrouw en hogere patiënttevredenheid. Toekomstige onderzoeken dienen zich te richten op het valideren en optimaliseren van deze voorspellers door middel van prospectieve studies in grotere patiëntengroepen. Daarnaast is er steeds meer twijfel over het categoriseren van de ernst van OSA op basis van vereenvoudigde maten zoals de AHI en de ODI, gezien deze waardes niet altijd overeenkomen met de zelf gerapporteerde symptomen van patiënten. Er blijft echter behoefte aan objectieve meetwaardes om de ernst van OSA en therapiesucces te beoordelen. In de toekomst is hierin mogelijk een rol weggelegd voor biomarkers geassocieerd met OSA, die mogelijk kunnen bijdragen aan de screening en monitoring van OSA.

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Appendices

List of abbreviations

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AASM	American academy of sleep medicine
AEs	Adverse events
AHI	Apnea-hypopnea index
AI	Apnea index
ANOVA	Analysis of variance
AP	Anteroposterior
AUC	Area under the curve
BMI	Body mass index
BRP	Barbed reposition pharyngoplasty
CCC	Complete concentric collapse
CGI	Clinical global impression
CI	Confidence interval
Co	Concentric
CPAP	Continuous positive airway pressure
CSA	Central sleep apnea
DISE	Drug-induced sleep endoscopy
ECG	Electrocardiography
EEG	Electroencephalography
EMG	Electromyography
ENT	Ear, nose, throat
EOG	Electrooculography
ESS	Epworth sleepiness scale
FOSQ	Functional outcomes of sleep questionnaire
ICSD	International classification of sleep disorders
IPG	Implanted pulse generator
IQR	Interquartile range
JM	Jaw thrust maneuver
La	Lateral
MAD	Mandibular advancement devices
MAM	Mandibular advancement maneuver
MMA	Maxillomandibular advancement
MRI	Magnetic resonance imaging
NC	Neck circumference
NPV	Negative predictive value
OAT	Oral appliance treatment
ODI	Oxygen desaturation index

OPT	Orthopantomography
OSA	Obstructive sleep apnea
PET	Patient experience with therapy
PG	Respiratory polygraphy
POSA	Positional obstructive sleep apnea
PPV	Positive predictive value
PSG	Polysomnography
PT	Positional therapy
RFTB	Radio frequent ablation of the tongue base
ROC	Receiver operating characteristic
SBD	Sleep-related breathing disorders
TCI	Target-controlled infusion
TMD	Temporomandibular dysfunction
TMJ	Temporomandibular joint
TORS	Transoral robotic surgery
UAS	Upper airway stimulation
UPPP	Uvulopalatopharyngoplasty
VOTE	Velum, oropharynx, tongue base, epiglottis

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About the author

Christianne Veugen was born on the 18th of December 1991 in Maastricht, the Netherlands. After graduation from the Gymnasium in 2010, she moved to Amsterdam to study medicine at the University of Amsterdam.

During her medical study she combined her interest in healthcare and traveling by spending some time abroad. She completed a nursing internship at the internal ward of the Sint Vincentius Ziekenhuis in Paramaribo, Suriname, and conducted a research internship at the Mahidol Oxford Research Unit (MORU) in Cambodia and Thailand. During this period, she authored her first article on submicroscopic *Plasmodium* prevalence in relation to malaria incidence in Western Cambodia.

In the final year of her medical studies, she decided to pursue a career in Otolaryngology and Head & Neck Surgery. She spent four months at the Department of Otolaryngology and Head & Neck Surgery in the Amsterdam UMC and initiated a research project in collaboration with the Department of Clinical Anatomy & Embryology focusing on the developmental origin of the auricle. Additionally, she spent two months at the Department of Otolaryngology and Head & Neck Surgery in the Flevoziekenhuis in Almere, co-authoring an article on the watchful waiting policy in tympanic membrane retractions.

In 2018, she obtained her medical degree and commenced work as Surgical resident at the Amstelland Hospital in Amstelveen. Towards the end of the same year, she started working as resident Otolaryngology at the Sint Antonius Hospital in Nieuwegein/Utrecht. Simultaneously, she initiated a PhD project on obstructive sleep apnea under the guidance of Dr. M.P. Copper and Prof. Dr. R.J. Stokroos, resulting in this thesis.

In 2021, she commenced her residency in Otolaryngology and Head & Neck Surgery at the UMC Groningen, under the supervision of Dr. R. Hofman, Dr. A.G.W. Korsten-Meijer and Prof. Dr. M.K.S. Hol. During her residency, she completed part of her training at the Ommelander Hospital in Scheemda, supervised by Dr. W.L. Valk. Currently, she is working at the Isala Hospital in Zwolle as part of her senior residency, under the supervision of Dr. D.A.E. Dietz de Loos and Dr. H. van Det-Bartels.

She currently lives in Amsterdam together with her partner, Christopher Tan.

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